CRITICAL CARE PHARMACY

PREPARATORY REVIEW AND RECERTIFICATION COURSE

2025

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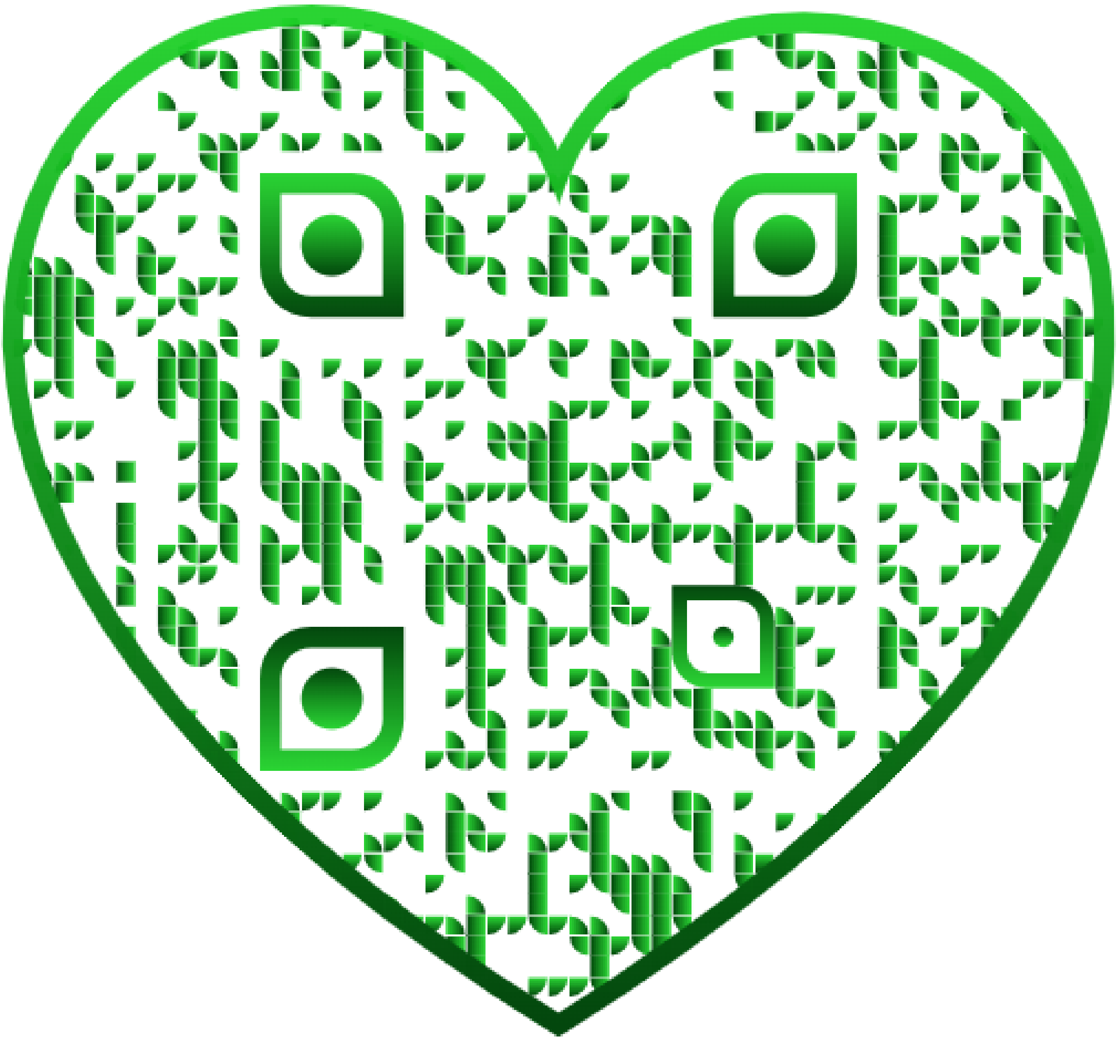

American College of Clinical Pharmacy and
American Society of Health-System Pharmacists

Critical Care Pharmacy Preparatory Review and Recertification Course

AMERICAN COLLEGE OF CLINICAL PHARMACY AND AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS

CRITICAL CARE PHARMACY PREPARATORY REVIEW AND RECERTIFICATION COURSE

2025 EDITION

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Director, Professional Development and Marketing: Joanna Gillette
Project Manager, Professional Development: Hannah Franzen
Senior Medical Editor: Kimma Sheldon-Old, PhD
Cover Design and Layout: Dane Anderson

For order information or questions, contact:
American College of Clinical Pharmacy
13000 W. 87th St. Parkway
Lenexa, KS 66215-4530
Phone: (913) 492-3311
accp@accp.com
http://www.accp.com

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PROGRAM GOALS AND TARGET AUDIENCE

The Critical Care Pharmacy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Critical Care Pharmacy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in critical care pharmacy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each topic.

FACULTY

***Designates Content Matter Experts for the Course**

Mahmoud A. Ammar, Pharm.D., MBA, FCCM, BCPS, BCCCP
Senior Critical Care Clinical Pharmacy Specialist
Yale New Haven Hospital
New Haven, Connecticut

Stephanie Bass, Pharm.D., FCCP, BCPS, BCCCP*
Medical ICU Clinical Pharmacist
Cleveland Clinic
Cleveland, Ohio

Grace E. Benanti, Pharm.D., BCCCP
Critical Care Clinical Pharmacist – Medical ICU
Loyola University Medical Center
Maywood, Illinois

Paige Garber Bradshaw, Pharm.D., BCCCP
Critical Care Clinical Pharmacy Specialist
UC Health – University of Cincinnati Medical Center;
Adjunct Associate Professor of Pharmacy Practice and Administrative Sciences
University of Cincinnati James L. Winkle College of Pharmacy
Cincinnati, Ohio

Christopher A. Droege, Pharm.D., FCCP, FASHP, FCCM
Manager, Clinical Pharmacy and Infusion Services
UC Health – University of Cincinnati Medical Center;
Adjunct Assistant Professor of Pharmacy Practice and Administrative Sciences
University of Cincinnati James L. Winkle College of Pharmacy
Cincinnati, Ohio

Julie E. Farrar, Pharm.D., BCCCP
Assistant Professor
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Megan E. Feeney, Pharm.D., BCCCP
Clinical Pharmacy Manager, ICU & Surgery
Boston Medical Center
Boston, Massachusetts

Gabrielle A. Gibson, Pharm.D., FCCM, BCPS, BCCCP*
Clinical Pharmacy Specialist
Barnes-Jewish Hospital
St. Louis, Missouri

Jamie Robenolt Gray, Pharm.D., FCCM, BCCCP
System Director of Medication Safety and Policy
Temple University Health System;
PGY1 Residency Program Director
Temple University Health System
Philadelphia, Pennsylvania

Ashley Hawthorne, Pharm.D., BCCCP
Assistant Clinical Professor
Auburn University Harrison College of Pharmacy
Mobile, Alabama

David M. Hill, Pharm.D., MS, FCCP, FCCM, BCPS, BCCCP
Clinical Pharmacist
Director of Burn Research
Regional One Health
Memphis, Tennessee

Mollie G. Lumpkin, Pharm.D., BCPS, BCCCP
Clinical Pharmacist
Cleveland Clinic
Cleveland, Ohio

Casey C. May, Pharm.D., FNCS, BCCCP
Associate Professor – Clinical
The Ohio State University College of Pharmacy;
Specialty Practice Pharmacist – Neurocritical Care
The Ohio State University Wexner Medical Center
Columbus, Ohio

Eric W. Mueller, Pharm.D., FCCP, FCCM*
Director, Acute Care and Infusion Pharmacy Services
UC Health-University of Cincinnati Medical Center & West Chester Hospital;
Adjunct Professor of Pharmacy Practice and Administration
University of Cincinnati
Cincinnati, Ohio

Sajni V. Patel, Pharm.D., BCCP
Clinical Pharmacy Coordinator, Cardiology Services
Clinical Pharmacy Specialist, Cardiac ICU
The University of Chicago Medicine
Chicago, Illinois

Gretchen L. Sacha, Pharm.D., FCCM, BCCCP*
Critical Care Clinical Pharmacist
Cleveland Clinic
Cleveland, Ohio

Jacob S. Schwarz, Pharm.D., MBA, FAzPA, BCIDP, BCPS, BCCCP
Critical Care Pharmacist
Mayo Clinic
Phoenix, Arizona

Keaton S. Smetana, Pharm.D., MBA, FCCM, FNCS
Clinical Pharmacy Manager
OhioHealth Riverside Methodist Hospital
Columbus, Ohio

Zachary R. Smith, Pharm.D., FCCP, FCCM, BCPS, BCCCP
Clinical Pharmacy Specialist; Critical Care, Pulmonary Hypertension
Henry Ford Hospital
Detroit, Michigan

Joanna L. Stollings, Pharm.D., FCCP, FCCM, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
Vanderbilt University Medical Center
Nashville, Tennessee

Joseph M. Swanson, Pharm.D., FCCP, FCCM
Professor of Clinical Pharmacy and Translational Science
Assistant Director of Experiential Education and International Programs
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Kyle A. Weant, Pharm.D., FCCP, BCPS, BCCCP
Clinical Assistant Professor-Emergency Medicine
Department of Clinical Pharmacy and Outcome Sciences, University of South Carolina College of Pharmacy
Columbia, South Carolina

Patrick M. Wieruszewski, Pharm.D., FCCM, BCCCP
Critical Care Pharmacist – Cardiothoracic Surgery & ECMO Program
Assistant Professor of Anesthesiology, Assistant Professor of Pharmacy – College of Medicine
Mayo Clinic
Rochester, Minnesota

Adrian Wong, Pharm.D., MPH, FCCP, FCCM, BCCCP*
Clinical Pharmacy Specialist, Medical ICU
Beth Israel Deaconess Medical Center
Boston, Massachusetts

FINANCIAL DISCLOSURES

In accordance with the Standards of Integrity and Independence in Accredited Continuing Education, ACCP/ASHP requires that all individuals in control of content disclose all financial relationships with ineligible companies. An individual has a relevant financial relationship if they have had a financial relationship with an ineligible company in any dollar amount in the past 24 months and the educational content that the individual controls is related to the business lines or products of the ineligible company.

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FACULTY DISCLOSURES

Advisory Board: Ashley Hawthorne (Vericel Corporation), Zachary R. Smith (Merck), Kyle A. Weant (GlaxoSmithKline)

Consultant: David M. Hill (Shionogi Inc, Innoviva Specialty Therapeutics), Gretchen L. Sacha (Wolters Kluwer), Patrick M. Wieruszewski (Wolters Kluwer/UpToDate, Viatris Inc)

Speaker/Speaker's Bureau: Stephanie Bass (Mallinckrodt Pharmaceuticals), Gabrielle A. Gibson (AstraZeneca), Ashley Hawthorne (Vericel Corporation), David M. Hill (Shionogi Inc, Innoviva Specialty Therapeutics)

Grants/Research: David M. Hill (Shionogi Inc, Access Pro Medical, Medline Industries LP, Trevena Inc)

Nothing to Disclose: Mahmoud A. Ammar, Grace E. Benanti, Paige Garber Bradshaw, Christopher A. Droege, Julie E. Farrar, Megan E. Feeney, Jamie Robenolt Gray, Mollie G. Lumpkin, Casey C. May, Eric W. Mueller, Sajni V. Patel, Jacob S. Schwarz, Keaton S. Smetana, Joanna L. Stollings, Joseph M. Swanson, Adrian Wong

REVIEWER DISCLOSURES

Speaker/Speaker's Bureau: Elise Metts (AbbVie)

Nothing to Disclose: Ola A. Adejuwon, Abdullah M. Alhammad, Shannon J. Allcron, Lolowa M. Alswaidan, Daniel Blee, Kimberly Brandt, Mark Brockway, Todd Brothers, Eugene N. Bush, Austin Camp, Justin S. Chung, Stephanie R.L. Ciapala, Alexis Nobel Crawford, Brynna Crovetto, Shereen Ahmad Dasuqi, Sonia Everhart, Seth Garner, Kristin Griebe, Payal K. Gurnani, Shannon Hasara, Lawahidh Hasham, Tudy Hodgman, Miranda Howland, Jessica Hu, Savannah L. Jones, Jennifer S. Lee, Melanie R. Madorsky, Keri Mills, Bethany Mocas, Christopher Oswald, Dipti Patel, Kerry Anne Rambaran, Alyssa Robertson, Alaina Shukdinas, Angela Slampak-Cindric, Alicia P. Surber, Elizabeth C. Taylor

---

All relevant financial relationships with ineligible companies listed have been mitigated.

All other planners, presenters, reviewers, ASHP and ACCP, and others with an opportunity to control content report no financial relationships relevant to this activity.

ACKNOWLEDGMENTS

Erik E. Abel, Pharm.D., BCPS
Director of Clinical Transformation
Highmark Health
Pittsburgh, Pennsylvania

Jerry Altshuler, Pharm.D., BCPS, BCCCP
Clinical Pharmacy Manager
Comprehensive Pharmacy Services
Hackensack Meridian Health
JFK Medical Center
Edison, New Jersey

Mahmoud A. Ammar, Pharm.D., FCCM, BCPS, BCCCP
Senior Critical Care Clinical Pharmacy Specialist
Yale New Haven Hospital
New Haven, Connecticut

Erin F. Barreto, Pharm.D., M.Sc., FCCM, FASN, BCPS, BCCCP
Associate Professor of Medicine and Pharmacy
Mayo Clinic
Rochester, Minnesota

Stephanie Bass, Pharm.D., FCCP, BCPS, BCCCP
Medical ICU Clinical Pharmacist
Cleveland Clinic
Cleveland, Ohio

Grace E. Benanti, Pharm.D., BCCCP
Critical Care Clinical Pharmacist - Medical ICU
Loyola University Medical Center
Maywood, Illinois

Scott T. Benken, Pharm.D., MHPE, FCCP, FCCM, BCPS-AQ Cardiology
Clinical Associate Professor
University of Illinois Chicago College of Pharmacy;
Clinical Pharmacist – Medical Intensive Care Unit
University of Illinois Health
Chicago, Illinois

Michael L. Bentley, Pharm.D., FCCP, FCCM, FNAP
Investigational Drug and Clinical Pharmacy Specialist
Department of Pharmacy
Carilion Clinic
Roanoke, Virginia

Brittany D. Bissell, Pharm.D., Ph.D., BCCCP
Assistant Professor
University of Kentucky College of Medicine;
Clinical Pharmacist
University of Kentucky Medical ICU
Lexington, Kentucky

Bradley A. Boucher, Pharm.D., FCCP, FNAP, MCCM
Professor of Clinical Pharmacy and Translational Science
University of Tennessee Health Science Center College of Pharmacy;
Associate Dean for Strategic Initiatives and Operations
Regional One Health
Memphis, Tennessee

Paige Garber Bradshaw, Pharm.D., BCCCP
Critical Care Clinical Pharmacy Specialist
UC Health – University of Cincinnati Medical Center;
Adjunct Associate Professor of Pharmacy Practice and Administrative Sciences
University of Cincinnati James L. Winkle College of Pharmacy
Cincinnati, Ohio

Gretchen M. Brophy, Pharm.D., FCCP, FCCM, FNCS, MCCM, BCPS
Professor of Pharmacotherapy & Outcomes Sciences and Neurosurgery
Virginia Commonwealth University
Medical College of Virginia Campus;
Neurocritical Care Clinical Pharmacist
Virginia Commonwealth University of Health
Richmond, Virginia

Mitchell Buckley, Pharm.D., FCCP, FCCM, FASHP, BCCCP
Clinical Pharmacy Specialist
Banner Health
Phoenix, Arizona

Henry Cohen, Pharm.D., FCCM, BCPP, BCGP
Professor of Pharmacy Practice
Arnold & Marie Schwartz College of Pharmacy and Health Sciences
Long Island University
Brooklyn, New York

Aaron Cook, Pharm.D., BCPS, BCCCP
Clinical Coordinator, Neuroscience-Pulmonary/Critical Care
Assistant Adjunct Professor, Pharmacy
University of Kentucky
Lexington, Kentucky

James C. Coons, Pharm.D., BCPS-AQ Cardiology
Associate Professor
University of Pittsburgh School of Pharmacy;
Clinical Pharmacist, Cardiology
PGY2 Cardiology Residency Program Director
UPMC Presbyterian Hospital
Pittsburgh, Pennsylvania

Mitchell James Daley, Pharm.D., FCCM, BCCCP
Market Clinical Pharmacy Specialist, Critical Care
Dell Seton Medical Center at the University of Texas;
Clinical Assistant Professor
Department of Surgery
Dell Medical School at The University of Texas
Austin, Texas

Christopher Allen Droege, Pharm.D., FCCP, FCCM, FASHP, BCCCP
Manager, Clinical Pharmacy and Infusion Services
University of Cincinnati Health – University of Cincinnati Medical Center;
Adjunct Assistant Professor of Pharmacy Practice and Administrative Sciences
University of Cincinnati James L. Winkle College of Pharmacy
Cincinnati, Ohio

Stephanie Dwyer Kaluzna, Pharm.D., BCCP
Clinical Assistant Professor
University of Illinois Chicago College of Pharmacy;
Cardiovascular Clinical Pharmacist
University of Illinois Hospital and Health Sciences System
Chicago, Illinois

Julie E. Farrar, Pharm.D., BCCCP
Assistant Professor
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Megan E. Feeney, Pharm.D., BCCCP
Clinical Pharmacy Manager, ICU & Surgery
Boston Medical Center
Boston, Massachusetts

Gabrielle A. Gibson, Pharm.D., BCPS, BCCCP
Clinical Pharmacy Specialist
Barnes-Jewish Hospital
St. Louis, Missouri

Jamie Robenolt Gray, Pharm.D., FCCM, BCCCP
System Director of Medication Safety and Policy
Temple University Health System;
PGY1 Residency Program Director
Temple University Health System
Philadelphia, Pennsylvania

Curtis E. Haas, Pharm.D., FCCP
Chief Pharmacy Officer
University of Rochester Medical Center
Rochester, New York

Lisa Hall Zimmerman, Pharm.D., FCCP, FCCM, BCPS, BCNSP, BCCCP
Clinical Pharmacy Specialist
Beaumont Hospital
Royal Oak, Michigan;
Adjunct Assistant Professor of Pharmacy Practice
Wayne State University
Eugene Applebaum College of Pharmacy and Health Sciences
Detroit, Michigan

Ashley Hawthorne, Pharm.D., BCCCP
Assistant Clinical Professor
Auburn University Harrison College of Pharmacy
Mobile, Alabama

David M. Hill, Pharm.D., FCCM, BCPS, BCCCP
Clinical Pharmacist
Director of Burn Research
Regional One Health
Memphis, Tennessee

Simon W. Lam, Pharm.D., M.Sc., FCCM, BCPS, BCCCP
Clinical Pharmacy Specialist
Cleveland Clinic
Cleveland, Ohio

Ishaq Lat, Pharm.D., FCCP, FCCM, BCPS, BCCCP
Director of Pharmacy
Shirley Ryan AbilityLab
Chicago, Illinois

Mollie G. Lumpkin, Pharm.D., BCPS, BCCCP
Clinical Pharmacist
Cleveland Clinic
Cleveland, Ohio

Casey C. May, Pharm.D., FNCS, BCCCP
Associate Professor – Clinical
The Ohio State University College of Pharmacy;
Specialty Practice Pharmacist – Neurocritical Care
The Ohio State University Wexner Medical Center
Columbus, Ohio

Eric W. Mueller, Pharm.D., FCCP, FCCM
Director, Acute Care and Infusion Pharmacy Services
UC Health-University of Cincinnati Medical Center & West Chester Hospital;
Adjunct Professor of Pharmacy Practice and Administration
University of Cincinnati
Cincinnati, Ohio

Diana Wells Mulherin, Pharm.D., FCCM, FASPEN, BCNSP, BCCCP
Clinical Pharmacy Specialist, Nutrition Support
Vanderbilt University Medical Center
Nashville, Tennessee

Megan E. Musselman, Pharm.D., M.Sc., BCPS, BCCCP
Clinical Pharmacy Specialist
Emergency Medicine/Critical Care
North Kansas City Hospital
Kansas City, Missouri

Andrea M. Nei, Pharm.D., FCCM, BCPS, BCCCP
Critical Care Pharmacist
Mayo Clinic Hospital – Rochester;
Assistant Professor of Pharmacy
Mayo Clinic College of Medicine & Science
Rochester, Minnesota

Sajni V. Patel, Pharm.D., BCCP
Clinical Pharmacy Coordinator, Cardiology Services
Clinical Pharmacy Specialist, Cardiac ICU
The University of Chicago Medicine
Chicago, Illinois

Sara Radparvar, Pharm.D., BCPS, BCCCP
Director of Clinical Pharmacy Services
The Mount Sinai Hospital
New York, New York

Gretchen L. Sacha, Pharm.D., FCCM, BCCCP
Critical Care Pharmacy Specialist
Cleveland Clinic
Cleveland, Ohio

Jacob S. Schwarz, Pharm.D., MBA, FAzPA, BCIDP, BCPS, BCCCP
Critical Care Pharmacist
Mayo Clinic
Phoenix, Arizona

Keaton S. Smetana, Pharm.D., MBA, FCCM, FNCS, BCCCP
Clinical Pharmacy Manager
OhioHealth Riverside Methodist Hospital
Columbus, Ohio

Zachary R. Smith, Pharm.D., FCCP, FCCM, BCPS, BCCCP
Clinical Pharmacy Specialist; Critical Care, Pulmonary Hypertension
Henry Ford Hospital
Detroit, Michigan

Joanna L. Stollings, Pharm.D., FCCP, FCCM, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
Vanderbilt University Medical Center
Nashville, Tennessee

Joseph M. Swanson, Pharm.D., FCCP, FCCM
Professor of Clinical Pharmacy and Translational Science
Assistant Director of Experiential Education and International Programs
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Eljim P. Tesoro, Pharm.D., FNCS, FCCM, BCCCP
Clinical Associate Professor
University of Illinois at Chicago College of Pharmacy;
Clinical Pharmacist, Neurocritical Care
University of Illinois Health
Chicago, Illinois

Edward T. Van Matre, Pharm.D., M.S., BCCCP
Assistant Professor
University of Tennessee Health Science Center College of Pharmacy
Memphis, Tennessee

Kyle A. Weant, Pharm.D., FCCP, BCPS, BCCCP
Clinical Assistant Professor
Department of Clinical Pharmacy and Outcome Sciences, University of South Carolina Pharmacy;
Emergency Medicine Clinical Pharmacy Specialist
Department of Pharmacy, Prisma Health-Midlands
Columbia, South Carolina

Patrick M. Wieruszewski, Pharm.D., FCCM, BCCCP
Critical Care Pharmacist – Cardiothoracic Surgery & ECMO Program
Assistant Professor of Anesthesiology, Assistant Professor of Pharmacy – College of Medicine
Mayo Clinic
Rochester, Minnesota

Adrian Wong, Pharm.D., MPH, FCCP, FCCM, BCCCP
Clinical Pharmacist, Medical ICU
Beth Israel Deaconess Medical Center;
Adjunct Associate Professor of Pharmacy Practice
MCPHS University
Boston, Massachusetts

Reviewers

The American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, and the authors would like to thank the following individuals for their reviews of the Critical Care Pharmacy Preparatory Review and Recertification Course, 2025 Edition.

Ola A. Adejuwon, Pharm.D., MPH, BCCCP, BCNSP
Clinical Pharmacy Leader in Critical Care
Houston Methodist Willowbrook Hospital;
Faculty Preceptor
University of Texas College of Pharmacy
Houston, Texas

Abdullah M. Alhammad, Pharm.D., BSc, BCPS, BCCCP
Associate Professor of Clinical Pharmacy
King Saud University;
Consultant Critical Care Pharmacist/Manager, Clinical Pharmacy Services/Drug and Poison Information Center
King Saud University Medical City
Riyadh, Saudi Arabia

Shannon J. Allcron, Pharm.D., BCPS, BCCCP
Critical Care Clinical Pharmacy Specialist
Owensboro Health Regional Hospital
Owensboro, Kentucky

Lolowa M. Alswaidan, MSc, BCCCP, SCC-CCP
Clinical Pharmacy Specialist
King Abdulaziz Medical City, Ministry of National Guard Health Affairs;
Joint Appointed Assistant Professor
King Saud bin Abdulaziz University for Health Sciences
Riyadh, Saudi Arabia

Daniel Blee, Pharm.D., BCCP, BCCCP
Clinical Cardiology Pharmacist
Kootenai Health
Coeur d'Alene, Idaho

Kimberly Brandt, Pharm.D., BCCCP
Clinical Pharmacy Specialist, Residency Program Director
Parma, Ohi

Mark Brockway, Pharm.D., BCPS, BCCCP, BCIDP, BCCP, BCEMP, AACC
Critical Care Pharmacist
EvergreenHealth Medical Center
Kirkland, Washington

Todd Brothers, Pharm.D., BCPS, BCCCP
Clinical Associate Professor of Pharmacy Practice
University of Rhode Island;
Clinical Pharmacy Specialist-Critical Care
Roger Williams Medical Center
Providence, Rhode Island

Eugene N. Bush, PhD, BCPS, BCCCP
Clinical Pharmacist, Critical Care
Vista Medical Center
Waukegan, Illinois

Austin Camp, Pharm.D., BCCCP
Associate Professor of Pharmacy Practice
Union University College of Pharmacy;
Critical Care Pharmacist
Jackson-Madison County General Hospital
Jackson, Tennessee

Justin S. Chung, Pharm.D., BCCCP
Clinical Pharmacist
University Medical Center of Southern Nevada
Las Vegas, Nevada

Stephanie R.L. Ciapala, Pharm.D., BCCCP
Clinical Pharmacy Specialist, Cardiothoracic/Vascular Surgery ICU
Cleveland Clinic
Cleveland, Ohio

Alexis Nobel Crawford, Pharm.D., FVSHP, BCPS, BCCCP
Assistant Professor
Virginia Commonwealth University School of Pharmacy;
Critical Care Clinical Pharmacist
Virginia Commonwealth University Health
Richmond, Virginia

Brynna Crovetto, Pharm.D., BCPS, BCCCP
Health Systems Pharmacist III
NYC Health + Hospitals/Bellevue Hospital Center
New York, New York

Shereen Ahmad Dasuqi, MScPharm, BCPS, BCCCP
Critical Care Clinical Pharmacist
King Saud University Medical City
Riyadh, Saudia Arabia

Sonia Everhart, Pharm.D., FCCM, BCPS, BCCCP
Clinical Pharmacy Specialist – Critical Care
Atrium Health
Charlotte, North Carolina

Seth Garner, Pharm.D., BCCCP
Trauma ICU Pharmacist
Atrium Health Wake Forest Baptist Health Medical Center
Winston-Salem, North Carolina

Kristin Griebe, Pharm.D., BCCCP
Clinical Pharmacy Specialist, Cardiothoracic Surgery/Cardiac ICU;
PGY1/PGY2 Pharmacotherapy Residency Program Director
Henry Ford Hospital
Detroit, Michigan

Payal K. Gurnani, Pharm.D., FCCM, BCPS, BCCCP
Clinical Pharmacy Specialist, Surgical-Liver ICU
Houston Methodist Hospital
Houston, Texas

Shannon Hasara, Pharm.D., BCCCP, BCEMP
Assistant Professor, Department of Pharmacotherapeutics & Clinical Research
University of South Florida Taneja College of Pharmacy
Tampa, Florida

Lawahidh Hasham, Pharm.D., MScPharm & Tox, BCPS, BCCCP, BCIDP, CPHQ
Clinical Pharmacist
THR Alliance
Fort Worth, Texas

Tudy Hodgman, Pharm.D., BCPS, BCCCP
Independent Consultant
Sierra Madre, California

Miranda Howland, Pharm.D., BCCCP
Pharmacy Manager
Northeast Georgia Medical Center – Habersham
Demorest, Georgia

Jessica Hu, Pharm.D., BCCCP
Clinical Assistant Professor
Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey;
Clinical Pharmacy Specialist, Critical Care
Robert Wood Johnson University Hospital Somerset
Somerville, New Jersey

Savannah L. Jones, Pharm.D., BCCCP
Critical Care Pharmacy Specialist
Atrium Health Pineville
Charlotte, North Carolina

Jennifer S. Lee, Pharm.D., BCPS, BCCCP
Critical Care/ED Pharmacy Manager
Inova Fairfax Medical Campus
Arlington, Virginia

Melanie R. Madorsky, Pharm.D., BCPS, BCCP, BCCCP
Clinical Pharmacy Specialist, Cardiac Care Unit
Memorial Hermann-Texas Medical Center
Houston, Texas

Elise Metts, Pharm.D., BCCCP
Emergency Medicine Clinical Pharmacy Specialist
University of Kentucky Chandler Medical Center;
Assistant Adjunct Professor
University of Kentucky College of Pharmacy
Lexington, Kentucky

Keri Mills, Pharm.D., BCPS, BCCCP, BCIDP
Clinical Pharmacy Specialist;
Antimicrobial Stewardship Coordinator
Baptist Memorial Hospital – Golden Triangle
Columbus, Mississippi

Bethany Mocas, Pharm.D., BCCCP
Clinical Pharmacy Specialist
Cleveland Clinic
Cleveland, Ohio

Christopher Oswald, Pharm.D., BCPS, BCCCP, DPLA
Manager, Clinical Pharmacy Services
Saint Alphonsus Health System
Boise, Idaho

Dipti Patel, Pharm.D., BCCCP, BCIDP, BCPS
Pharmacist, Clinical
Southern Regional Medical Center
Riverdale, Georgia

Kerry Anne Rambaran, Pharm.D., BCPS, BCCCP, BCEMP
Emergency Medicine Clinical Specialist
Scripps Mercy Hospital
San Diego, California

Alyssa Robertson, Pharm.D., BCPS, BCCCP, BCEMP
Clinical Pharmacist Specialist
WellSpan York Hospital
York, Pennsylvania

Alaina Shukdinas, Pharm.D., BCCCP
Medical Intensive Care Clinical Pharmacist
Atrium Health Wake Forest Baptist
Winston-Salem, North Carolina

Angela Slampak-Cindric, Pharm.D., FCCM, BCPS, BCCCP
Coordinator, Critical Care and Emergency Medicine;
Director, PGY2 Critical Care Pharmacy Residency Program
Geisinger Medical Center
Danville, Pennsylvania

Alicia P. Surber, Pharm.D., BCPS, BCCCP, BCCP, BCEMP
Clinical Pharmacist
Saint Alphonsus Regional Medical Center
Boise, Idaho

Elizabeth C. Taylor, Pharm.D., BCCCP
Clinical Assistant Professor;
Critical Care Pharmacy Specialist
Marshall University School of Pharmacy
Huntington, West Virginia

In addition to the reviewers above, all chapters were reviewed by 1 or more of ACCP/ASHP’s Course Content Matter Experts.

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American College of Clinical Pharmacy and
American Society of Health-System Pharmacists

Critical Care Pharmacy Preparatory
Review and Recertification Course

Evolution and Validation of Practice Standards, Training, and Professional Development

Eric W. Mueller, Pharm.D., FCCP, FCCM

UC Health-University of Cincinnati Medical Center
University of Cincinnati
Cincinnati, Ohio

Evolution and Validation of Practice Standards, Training, and Professional Development

Eric W. Mueller, Pharm.D., FCCP, FCCM

UC Health-University of Cincinnati Medical Center
University of Cincinnati
Cincinnati, Ohio

Learning Objectives

1. Describe landmark events in the evolution of critical care pharmacy as a specialty, including summarizing key published documents and primary evidence validating critical care pharmacy as a specialty.
2. Identify the core knowledge areas for pharmacists caring for critically ill patients.
3. Outline criteria for credentialing, conventional training pathways and mentorship, and standards of practice for clinical pharmacy in the critical care practice environment.
4. Develop an approach to conducting a gap analysis relative to the principles and values of team-based care in a local critical care practice environment.
5. Develop an approach to lifelong professional learning to maintain competency in critical care pharmacy practice using the principles of continuing personal professional development.
6. Identify the avenues and processes for contributing to the critical care body of knowledge as a presenter, author, or peer reviewer.

Abbreviations in This Chapter

ACCM	American College of Critical Care Medicine
ACCP	American College of Clinical Pharmacy
ACLS	Advanced cardiac life support
ASHP	American Society of Health-System Pharmacists
BPS	Board of Pharmacy Specialties
CE	Continuing education
CPD	Continuing professional development
CPE	Continuing pharmacy education
ICU	Intensive care unit
NCS	Neurocritical Care Society
PDP	Personal development plan
SCCM	Society of Critical Care Medicine

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. Which is the journal that, in 1982, was the first to publish a critical care therapeutics column?
    A. *Drug Intelligence and Clinical Pharmacy.*
    B. *Pharmacotherapy.*
    C. *Chest.*
    D. *Heart & Lung.*

2. The scope of pharmacy practice within the intensive care unit (ICU) was outlined by two task forces focused on models of critical care delivery, the definition of an intensivist, and the practice of critical care medicine within three different proposed models in 2001. Which best depicts the professional organization that formed these two task forces?
    A. National Academy of Medicine (formerly Institute of Medicine).
    B. American College of Clinical Pharmacy (ACCP).
    C. American College of Critical Care Medicine (ACCM).
    D. Clinical Pharmacy and Pharmacology Section of the Society of Critical Care Medicine (SCCM).

3. Which best depicts the medical event that has been documented to be associated with a lower mortality in ICUs with clinical pharmacists compared with ICUs without clinical pharmacists?
    A. Corrected QT (QTc)-interval prolongation.
    B. Preventable adverse drug interactions.
    C. Drug-drug interactions.
    D. Thromboembolic/infarction-related events.

4. Which best describes what is deemed a core knowledge base area for pharmacists caring for critically ill patients?
    A. Nephrology.
    B. Dermatology.
    C. Rheumatology.
    D. Obstetrics.

5. Which most accurately reflects the journal that published a landmark study documenting a decrease in preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds?
    A. *New England Journal of Medicine.*
    B. *Lancet.*
    C. *Journal of the American Medical Association.*
    D. *Annals of Internal Medicine.*

6. There were eight American Society of Health-System Pharmacists (ASHP)-accredited critical care pharmacy residencies in 2001. Which annual absolute value represents the approximate increase in ASHP-accredited critical care residencies between 2001 and 2021?

   A. 5.
   B. 8.
   C. 12.
   D. 15.

7. Which best reflects the current conventional or preferred postgraduate training pathway to clinical pharmacy practice in an ICU providing level I services?

   A. Postgraduate year 1 (PGY1) residency with focused critical care rotations.
   B. PGY1 residency followed by on-the-job mentored training.
   C. PGY1 and PGY2 critical care residency.
   D. PGY1 and critical care traineeship.

8. When considering the five principles of team-based health care delineated in the Institute of Medicine (now National Academy of Medicine) discussion paper, which of the other four principles is effective communication most tightly linked to?

   A. Shared goals.
   B. Clear roles.
   C. Mutual trust.
   D. Measurable processes and outcomes.

9. Which statement is most accurate concerning the mentor-mentee relationship as it pertains to the training and development of critical care pharmacists?

   A. Formal mentoring relationships are restricted to residency and fellowships.
   B. Voluntary relationships that evolve and develop through mutual interests have the greatest likelihood of success.
   C. Mentored training programs are the only reliable pathway for the nonconventional training of critical care pharmacists.
   D. Most successful critical care pharmacists have a single relevant mentor-mentee relationship during their training and development.

10. Which is the most accurate description of the relationship between the continuing pharmacy education (CPE) and the continuing professional development (CPD) of clinical pharmacists?

    A. CPE and CPD are two distinctly different processes for continuing development.
    B. CPD is an individualized, self-directed, and iterative process of development that replaces traditional CPE.
    C. CPE is strictly a didactic process, whereas CPD incorporates many different learning strategies and techniques.
    D. CPD is an individualized, self-directed process that typically incorporates relevant CPE as one of the learning strategies.

11. Which statement is most accurate relative to the recently published standards of care and standardized process of care for clinical pharmacy when considering critical care pharmacy practice?

    A. ICUs are highly individualized practice environments that cannot easily conform to broad-based, discipline-wide standards.
    B. Critical care pharmacists have knowledge and skill sets that are specific to their practice style and environment and are not consistent with the standards.
    C. The standards of care and standardized process of care are very consistent with critical care pharmacy practice standards and expectations.
    D. The standard process of care, which has evolved around the “provider status” efforts, is primarily applicable to the ambulatory, primary care environment of practice.

12. Which is the best example of an audience that has not traditionally been an important focus of critical care pharmacists’ educational and teaching efforts?

    A. Patients and families.
    B. Pharmacy students.
    C. Critical care physicians.
    D. Critical care nurses.

13. As part of the reflection stage of the CPD process, which would be the best example of an episodic opportunity for self-assessment?
    - A. An annual 360-degree peer evaluation providing feedback that your coworker believes you do not contribute adequately on departmental initiatives.
    - B. Recognition that the usual approach to training and assessing a challenging student on rotation was ineffective.
    - C. A self-evaluation of the past year's accomplishments for your direct supervisor.
    - D. An annual performance evaluation with specific goals for the coming year.

14. Which would be considered the most valid reason for recommending the rejection of a manuscript as a scientific reviewer?
    - A. Poor syntax and word choices.
    - B. A methodological flaw that results in incorrect data.
    - C. A disagreement concerning the statistical analysis presented in the manuscript.
    - D. Results presented in the abstract that are inconsistent with results presented in a table.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 2: Therapeutic and Patient Management
    a. Task C: 5
2. Domain 3: Professional Practice
    a. Task A: 3, 7
    b. Task B: 1, 2, 4, 5

I. LANDMARK EVENTS IN CRITICAL CARE MEDICINE/PHARMACY

A. First ICU: Three-Bed Neurosurgical Unit in Baltimore, Maryland (1930s) (Ann Pharmacother 2006;40:612-8)

B. First Pharmacists Assigned to ICUs in a Limited Number of Hospitals – Occurred in the late 1960s (Ann Pharmacother 2006;40:612-8)

C. Establishment of several Critical Care Pharmacists ICU Practices (in or around the 1970s; clinical research conducted in a wide array of therapeutic specialty areas [e.g., pharmacokinetics, infectious diseases, nutrition support, ACLS]) (Ann Pharmacother 2006;40:612-8; Practice of Critical Care Pharmacy, Rockville, MD: Aspen Publications, 1985)
   1. Cardiovascular ICUs
   2. Pediatric/neonatal ICUs
   3. Medical ICUs
   4. Emergency medicine
   5. Trauma
   6. Surgical ICUs
   7. Neurosurgical ICUs

D. Formation of SCCM with 100 Members (1970)
   1. Multidisciplinary model stressed by founding SCCM President Max Harry Weil, M.D.
   2. Subsequent inclusion of pharmacists as permanent members of the SCCM governing council

E. Emergence of Critical Care Specialty Journals and Publications
   1. *Heart & Lung* (1972)
   2. *Intensive Care Medicine* (1972)
   3. *Critical Care Medicine* (1973)
   4. *Critical Care Clinics* (1984)
   5. Critical care therapeutics column in *Drug Intelligence and Clinical Pharmacy* (1982)
   6. First critical care pharmacy textbook: *Critical Care Pharmacy* (1985)

F. Formation of Critical Care Pharmacists Specialty Groups
   1. SCCM Clinical Pharmacy and Pharmacology Section (1989)
   2. ACCP Critical Care Practice and Research Network (PRN) (1992)
   3. Neurocritical Care Society (NCS), Pharmacy Section (circa 1999)

II. VALIDATION OF CRITICAL CARE PHARMACY AS A SPECIALTY

A. Chapter Titled "Role of the Pharmacist in Caring for the Critically Ill Patient," Published in The Pharmacologic Approach to the Critically Ill Patient, 3rd ed. Baltimore, MD: Williams & Wilkins, 1994:156-66.

B. Publication of "Position Paper on Critical Care Pharmacy Services" (Crit Care Med 2000;28:3746-50); establishment of three levels of pharmacy services (fundamental, desirable, optimal) for the provision of pharmaceutical care in critically ill patients; major update in 2020 with recommendations simplified to essential and desirable. Statements and recommendations categorized as follows: Patient Care (n=34), Quality Improvement (n=21), Research/Scholarship (n=9), Training Education (n=10), and Professional Development (n=8) (Crit Care Med 2020;48:1375-82) (see Table 1 for details).

C. SCCM Recognition of Critical Care Pharmacists as an Integral Member of the Multidisciplinary Team Together with Physicians, Nurses, and Respiratory Therapists (Crit Care Med 2001;29:2007-19)

D. Scope of Pharmacy Practice Within ICU Outlined by Two ACCM Task Forces: Models of critical care delivery and definition of an intensivist and the practice of critical care medicine within three different proposed models (critical care pharmacy and pharmacist services deemed "essential" within level I critical care centers as endorsed by ACCM (Crit Care Med 2003;31:2677-83) (see specifics that follow)

E. Awarding of FCCM Status by ACCM: 221 pharmacists from an overall total of around 1440 (2024); nine of a total of 91 MCCMs (Master Critical Care Medicine) (2024); awarding FNCS status by the NCS (n=22) Receipt of Several Honors and Awards by Critical Care Pharmacists Within SCCM, ACCM, ACCP, and NCS. Below are some examples.
   1. SCCM/ACCM: Distinguished Investigator Award, Shubin-Weil Master Clinician, Excellence in Bedside Teaching Award, Distinguished Service Award
   2. ACCP: Russell R. Miller Award, Paul F. Parker Medal, Clinical Practice Award, Robert M. Elenbaas Service Award, Education Award
   3. Creation of the Joseph F. Dasta Critical Care Pharmacy Outcomes Research Grant by the Clinical Pharmacy and Pharmacology Section of SCCM (2000); Barry A. Shapiro Memorial Award for Excellence in Critical Care Management

F. Leadership Roles in Major Multidisciplinary and Pharmacy Organizations
   1. SCCM: Presidents Judith Jacobi (2010), Sandra L. Kane-Gill (2022)
   2. ACCP: Presidents Robert Elenbaas, Barbara Zarowitz, Bradley Boucher, Curtis Haas, Judith Jacobi, Brian Erstad, Jimmi Hatton Kolpek
   3. NCS: President Gretchen Brophy (2017-2018)
   4. ASHP: President: Thomas J. Johnson (2020)

G. Standards for Neurologic Critical Care Units: Inclusion of dedicated pharmacists on the neurocritical care team (Neurocrit Care 2018;29:145-60)

III. CRITICAL CARE PHARMACY GROWTH

A. SCCM Membership: Over 16,000 total; over 2300 with pharmacy credentials. ACCP Critical Care PRN: over 1600 (June 2023)

B. Board Certified Critical Care Pharmacists (BCCCPs): Around 4234 (2023 BPS Annual Report [http://books.bpsweb.org/books/npko/#p=26])

C. Pharmacist Provision of Direct Patient Care Services: 62.2% of ICUs responding to hospital survey sent to pharmacy directors identified by the American Hospital Association as having an ICU pharmacist (Ann Pharmacother 2006;40:612-8)

IV. STUDIES DOCUMENTING THE ASSOCIATION OF CRITICAL CARE PHARMACY SERVICES WITH FAVORABLE HEALTH CARE OUTCOMES

A. Reduction in Drug Costs in ICU with the Inclusion of a Pharmacist as a Member of the Multidisciplinary Team

1. Medical-surgical ICU: Annual savings of $67,664 in 1994 (Crit Care Med 1994;22:1044-8)
2. Several other studies in a wide range of ICU settings (see Intensive Care Med 2003;29:691-8)
3. Burn ICU: Annual savings of $22,162 in 2003 (J Burn Care Res 2006;310-13)
4. Neurosurgical ICU: Reduction in pharmacy acquisition costs from $4833 to $3239 per patient after the addition of a pharmacist to the neurosurgery team; reduction in ICU days from 8.56 to 7.24 days ($p=0.003$) (Neurosurgery 2009;65:946-50; discussion 950-1)
5. Scoping review conducted for cost avoidance generated by clinical pharmacists on interventions performed in an ICU or emergency department identified 38 distinctive categories (Pharmacotherapy 2019;39:215-31). Across 55,926 interventions, estimated cost avoidance was $418.48 per intervention and $845.49 per patient. Overall ratio of cost avoidance/pharmacist salary was between $3.3:1 and $9.6:1 (Crit Care Explor 2021;3:e0594).
6. Multicenter, observational cohort study in critically ill adult patients across a 25-hospital integrated health care system evaluating telehealth critical care pharmacist services in 8-hour shifts, 7 days a week, found that pharmacists documented 2838 interventions associated with $1,664,254 gross cost avoidance over 2 years. Expense:cost avoidance ratio was 4.5:1 (Crit Care Explor 2023;5:e0839).

B. Reduction in Adverse Drug Effects/Drug-Drug Interactions

1. Decrease in preventable adverse drug effects after the inclusion of a pharmacist on interdisciplinary medical ICU rounds: 66%, ($p<0.001$) (JAMA 1999;282:267-70); supported by meta-analysis of three studies (odds ratio (OR) 0.23, 95% confidence interval (0.11, 0.48) (J Crit Care 2015;30:1101-06). Reduced; preventable and nonpreventable adverse drug events (OR 0.26, 95% CI (0.15, 0.44), $p<0.0001$ and OR 0.47, 95% CI (0.28, 0.77, $p=0.003$, respectively) (Crit Care Med 2019;47:1243-50).
2. Decreased incidence of QTc-interval prolongation with ICU monitoring by a pharmacist using a standard algorithm: 19% versus 39% ($p=0.006$) (Ann Pharmacother 2008;42:475-82)
3. Reduction in drug-drug interactions by 65% ($p<0.01$) in medical ICUs with a pharmacist (J Crit Care 2011;26:104.e101-106)

C. Improvement in Infectious Diseases Morbidity, Mortality, and Costs (Crit Care Med 2008;36:3184-9)

1. Mortality in ICUs without clinical pharmacists than in ICUs with clinical pharmacists: 23.6% higher for nosocomial-acquired infections in ICUs without clinical pharmacists ($p<0.001$), 16.2% higher for community-acquired infections in ICUs without clinical pharmacists ($p=0.008$), 4.8% higher for sepsis in ICUs without clinical pharmacists ($p\leq0.008$)
2. Longer length of stay for ICUs without clinical pharmacists than for ICUs with clinical pharmacists: 7.9% for nosocomial-acquired infections in ICUs without clinical pharmacists ($p<0.001$), 5.9% for community-acquired infections in ICUs without clinical pharmacists ($p=0.03$), 8.1% for sepsis in ICUs without clinical pharmacists ($p<0.001$)
3. Increased Medicare billing in ICUs without clinical pharmacists compared with ICUs with clinical pharmacists: 12% for nosocomial-acquired infections in ICUs without clinical pharmacists, 11.9% for community-acquired infections in ICUs without clinical pharmacists, 12.9% for sepsis in ICUs without clinical pharmacists ($p<0.001$)

D. Improvement in Thromboembolic and Infarction-Related Event (TIE) Clinical and Economic Outcomes (Pharmacotherapy 2009;29:761-8)
   1. Mortality increased in ICU patients with TIE without clinical pharmacy services compared with ICU patients with clinical pharmacy services: 37%, (p<0.0001).
   2. Bleeding complications increased by 49% (p<0.001), with 39% more patients receiving transfusions (p=0.006) in ICUs without clinical pharmacy services.
   3. Length of ICU stays and costs were significantly higher in patients with TIE in ICUs without clinical pharmacy services.

E. Meta-Analysis of 14 Studies of Critical Care Pharmacists as Member of Multidisciplinary Team (Crit Care Med 2019;1243-50)
   1. Reduced mortality: OR 0.78, 95% CI (0.73-0.83, p<0.00001)
   2. LOS reduction: mean -1.33 days, 95% CI (-1.75, -0.90), p<0.00001)

F. Impact of ICU Protocols on Patient Outcomes
   1. Significant improvement in sedation and analgesia monitoring targets with the use of protocol versus empiric therapy (p≤0.01); no difference in length of ICU stay (Pharmacotherapy 2000;20:662-72)
   2. Pharmacist-enforced ICU sedation protocol reduced mechanical ventilator duration as well as ICU and hospital length of stay (p<0.001) (Crit Care Med 2008;36:427-33)
   3. Improvement in mortality with inclusion of clinical pharmacist after multicomponent intervention in tertiary care in a medical ICU (also included increase in ICU beds, larger rooms, 24-hour critical care specialist coverage, decrease in respiratory therapist/patient ratio) (Crit Care Med 2011;39:284-93)
      a. ICU mortality decrease from 18.4% to 14.9% (p=0.006), hospital mortality decrease 25.8% to 21.7% (p=0.005)
      b. Increase in median ICU length of stay; no difference in hospital length of stay
      c. Increase in median 28-day ventilator-free days in mechanically ventilated patients
      d. Mean decrease in daily dosing of fentanyl and lorazepam
   4. Pharmacist management of pain, agitation, and delirium in ICU through multidisciplinary bundle; 46% reduction in continuous sedation, reduction in ICU and hospital length of stay (Am J Health-Syst Pharm 2017;74:253-62); systematic review of pharmacist-led interventions on pain, agitation, and delirium in mechanically ventilated adults (J Am Coll Clin Pharm 2023;6:1041-52).
   5. Pharmacist involvement in multidisciplinary initiative to reduce sepsis-related mortality in ICU (i.e., “Code Sepsis”); reduction in mean time from sepsis screen to antibiotic administration from 427 minutes to 31 minutes (Am J Health-Syste Pharm 2016;73(3):143-9)
   6. Leadership role in developing clinical practice guidelines for preventing and managing pain, agitation/sedation, delirium, immobility, and sleep disruption in adult critically ill patients (PADIS Guidelines) (Crit Care Med 2002;30:119-41; Crit Care Med 2018;46:e825-73) and clinical practice guidelines for sustained neuromuscular blockade in critically ill adults (Crit Care Med 2016;44:2079-103).
   7. Before and after study of critical care pharmacist interventions on drug therapy and clinical strategies: Reduction in hospital length of stay (3.7 days, p<0.001), ICU length of stay (1.4 days, p<0.01), duration of mechanical ventilation (1.2 days, p<0.01), hospital costs per stay (2560 euros, p<0.001); no impact on mortality. (Crit Care Med 2018;46:199-207)
   8. Retrospective cohort study of albumin use in critically ill patients at single academic medical center: Reduction in inappropriate albumin use (50.9%, p<0.001), total annual cost savings greater than $355,000. (Ann Pharmacotherapy 2020;54:105-112).

V. PRACTICE STANDARDS FOR CRITICAL CARE PHARMACY

A. Standards of Practice for Clinical Pharmacists (J Am Coll Clin Pharm 2023;6:1156-9): The Standards of Practice for Clinical Pharmacists were published by ACCP, incorporating a standardized process of care endorsed by all major pharmacy organizations. This document defines expectations of clinical pharmacists delivering comprehensive medication management in team-based, collaborative practice settings, including the ICU.

1. Qualifications
    a. Licensed pharmacists
    b. Advanced education, training, and experience
        i. Advanced, accredited residency in critical care pharmacy (PGY2);
        ii. Fellowship in critical care research; or
        iii. Equivalent, relevant clinical experience
    c. Clinical and personal competencies to practice in a team-based collaborative environment
    d. Board certification
2. Process of care
    a. Collection of patient information
    b. Assessment of medication regimen
    c. Development of a plan of care for medication optimization
    d. Implementation of the plan of care
    e. Follow-up evaluation and medication monitoring
3. Documentation
    a. Medication history
    b. Active problem list with assessment
    c. Plan of care to achieve medication optimization
4. Collaborative, team-based care and privileging
5. Professional development and maintenance of competence
    a. Board certification and recertification
    b. CPE
    c. Maintenance of licensure
    d. Participation in formal and informal development activities
6. Professionalism and ethics – Demonstrate the traits of:
    a. Responsibility
    b. Commitment to excellence
    c. Respect for others
    d. Honesty and integrity
    e. Care and compassion for others
    f. High ethical standards
    g. Legal and regulatory compliance
7. Research and scholarship
8. Other
    a. Education and training
    b. Mentorship
    c. Management and leadership
    d. Policy and service development and implementation
    e. Consultation
    f. Performance/Quality improvement

B. Scope of Critical Care Pharmacy Services (Crit Care Med 2020;48:1375-82; Position Paper on Critical Care Pharmacy Services [a joint effort of SCCM, ACCP, and ASHP])
  1. The task force provided 82 recommendation statements across five distinct domains (see Table 1 for details):
    a. Patient Care (n=34)
    b. Quality Improvement (n=21)
    c. Research/Scholarship (n=9)
    d. Training/Education (n=10)
    e. Professional Development (n=8)
  2. Gradations of pharmacy practice
    a. Essential: These are practice recommendations that are considered vital to the provision of pharmacy care to ICU patients.
    b. Desirable: Offers recommendations that are more specialized and specific to the ICU beyond the essential recommendations
    c. Essential versus desirable recommendation statements are further categorized based on the level of ICU care being provided (see section V.D.1 in the text that follows for descriptions of level I, II, and III ICUs)

C. Critical Care Pharmacist as Educator: The critical care pharmacist has several educational missions and obligations (Pharmacotherapy 2011;31:135e-175e; Ann Pharmacother 2006;40:612-8; Pharmacotherapy 2002;22:1484-8; Crit Care Med 2000;28:3746-50 ; Crit Care Med 2020;48:1375-82), and teaching methods and techniques vary depending on intended audience and content. The clinical pharmacist must develop comfort and expertise with a wide range of teaching styles and techniques to be successful as an educator in the ICU setting.
  1. Pharmacy students and residents: Content has to be at a level appropriate to learners who may or may not have a primary interest in critical care. Active learning strategies must be incorporated with didactic approaches that are more traditional. For this audience, the clinical pharmacist has primary responsibility for assessment/grading.
    a. Clinical practice training
      i. Role modeling (I do, you watch)
      ii. Coaching (I do, you help … then … you do, I help)
      iii. Mentoring (You do, I watch)
      iv. Facilitating (you do, I monitor)
    b. Case-based teaching (point-of-care teaching)
    c. Hands-on demonstrations of equipment, technology, and devices used in the ICU
    d. Clinical conferences/topic discussions
    e. Assigned readings
    f. Journal club
    g. Quality improvement projects
    h. Writing assignments
      i. Case reports
      ii. Guideline/protocol development
      iii. Pharmacy and therapeutics (P&T) monographs
    i. Drug information response
    j. Medication use evaluations

2. Critical care team: More heavily focused on the specifics of critical care therapeutics. Content and sophistication will vary depending on audience (e.g., physicians vs. nurses). Audience is assumed to have a primary interest in critical care.
    a. Case-based, point-of-care teaching (bedside rounds)
    b. Didactic teaching
        i. Teaching rounds/conferences
        ii. In-service education
        iii. Grand rounds
        iv. Basic science lectures
    c. Critical care–specific journal club
    d. Collaboration on guidelines/protocols
    e. Quality improvement projects
3. Pharmacist colleagues: May not have a primary focus or interest in critical care. Content may be focused on specific pharmacotherapeutic issues (e.g., pharmacokinetic principles in the critically ill) that often arise during cross-coverage. May include pharmacists taking a nonconventional path to critical care practice.
    a. Didactic lectures (e.g., clinical conferences, topic-specific lectures)
    b. Hands-on demonstration of equipment, technology, and devices used in the ICU
    c. Case-based, point-of-care teaching
    d. Journal club
    e. Competency-based programs – Lead to credentialing according to demonstrated skills
4. Other trainees: Often includes a mix of backgrounds and interests (e.g., critical care fellows, anesthesia residents, medicine residents, emergency department (ED) residents, fourth-year medical students, nursing students, advanced-practice provider (APP) students, and dietary students). Content has to be appropriate for the predominant audience and baseline understanding of the topic.
    a. Didactic lectures
        i. Teaching rounds
        ii. Clinical conferences
    b. Point-of-care teaching – Bedside rounds
5. Patients and families: With an increasing emphasis on patient and family satisfaction and a greater involvement of the patient and family in shared decision-making, the need has increased for critical care pharmacists to be available as resources and provide education to patients and families about common medications and expected response in the ICU. Another emerging area of critical care pharmacist involvement is patient and family care and education in post-ICU clinics to address the challenges associated with post-ICU care for those who survive their ICU admission. The SCCM-sponsored THRIVE initiative promotes the growth of these interprofessional clinics.
    a. Techniques
        i. Simple language, basic content
        ii. Teach-back technique to assess understanding
        iii. Frequent reinforcement
        iv. Motivational interviewing techniques
        v. Open-ended questions to understand what is important to the patient and family
    b. Content
        i. Medications being initiated in the ICU
        ii. Why the medication is being used – Have goals different from home medications
        iii. What to expect – Effects, adverse effects, changes in patient interaction, etc.
        iv. Expected duration of new medications
        v. What factors are monitored to see whether medications are helping or hurting

D. Critical Care Services (Crit Care Med 2003;31:2677-83): ACCM recommended critical care services and personnel according to the level of care being provided. ICUs were defined as levels I, II, and III.

1. Levels of ICU services
    a. Level I
        i. Comprehensive critical care for a wide variety of patient populations with a high level of specialization
        ii. Requires broad range of comprehensive support, including pharmacy services, respiratory therapy, clinical nutrition, pastoral care, and social services
        iii. Often fulfills an academic mission
    b. Level II
        i. Comprehensive critical care but may not provide care for certain patient populations
        ii. Must have transfer protocols in place for patients with special needs
        iii. Comprehensive support services must be available.
        iv. May or may not have an academic mission
    c. Level III
        i. Provides stabilization, but has limited ability to provide comprehensive critical care
        ii. Must have transfer protocols in place for patients requiring level I and II critical care services
        iii. Support services are often limited in scope.
2. Critical care pharmacy services (level I and II ICUs)
    a. Reiterates pharmacist and pharmacy services defined in 2000 guideline (Crit Care Med 2000;28:3746-50)
    b. Emphasizes the importance of clinical pharmacists as required members of the patient care team
    c. Qualifications and competence of the critical care pharmacist in ICU therapeutics are defined as essential. Acknowledges several pathways, including advanced degrees, residency, fellowship, and other specialized practice experiences.
    d. ICUs with an academic mission should provide protected time for pharmacist participation in scholarly activities and appropriate knowledge and skills to provide education to critical care nurses, physician trainees, and physicians.
    e. Nonacademic centers should provide time for maintenance of competence and maintain current certification.

E. Principles and Values of Team-Based Health Care

1. SCCM and ACCP have long promoted the team-based care model for critical care as a standard, including clinical pharmacists as an essential staff member (Crit Care Med 2006;34(3 suppl):S46-51).
2. An Institute of Medicine (now National Academy of Medicine) discussion paper delineated the core principles and values of highly functioning interprofessional health care teams (see https://nam.edu/wp-content/uploads/2015/06/VSRT-Team-Based-Care-Principles-Values.pdf).
    a. Definition of team-based care: *Team-based health care is the provision of health services to individuals, families, and/or their communities by at least two health providers who work collaboratively with patients and their caregivers—to the extent preferred by each patient—to accomplish shared goals within and across settings to achieve coordinated, high-quality care.*
    b. Five personal values of effective members of high-functioning teams:
        i. Honesty: Includes effective, transparent communication. Essential to building mutual trust.
        ii. Discipline: Each team member carries out roles and responsibilities in a highly disciplined approach, even when inconvenient or difficult.
        iii. Creativity: Maintains excitement around addressing new and difficult challenges. Seeing opportunity in both successes and failures

        iv. Humility: Equal respect of all members, regardless of level of training or role – Not tied to traditional hierarchical thinking in health care. Recognizes that all members of the team are susceptible to mistakes.
        v. Curiosity: Dedicated to reflection and continuous improvement
    c. Five principles of team-based health care
        i. Shared goals: Clearly articulated, understood, and supported goals are established by the team that are consistent with the patient and family wishes. The patient and family are actively involved in establishing the goals of care as members of the team.
        ii. Clear roles: Each team member's functions, responsibilities, and accountabilities are clearly established and understood by the team. Efficiency and logical division of labor are achieved. Although autonomy is important, flexibility of roles and collaboration exist as needed.
        iii. Mutual trust: Establishing and maintaining trust, as well as openness to address questions about or breaches of trust, are essential. Mutual trust permits individual team members to function to their highest potential and rely on other team members to follow through on their commitments.
        iv. Effective communication: Tightly linked to mutual trust. The team has consistent channels for candid and complete communication by all team members and in all situations.
        v. Measurable processes and outcomes: The team develops and implements accurate and timely measures of successes and failures and uses the results to track and improve performance. Measures fall into two categories: Process/outcome measures and measures of team function. This principle is typically the most challenging for a team to implement and sustain effectively.

3. Critical care teams – Gap analysis: When considering the core principles of team-based care, critical care team members should evaluate their team structure and performance against these five principles. Effective teams are much more than patient care rounds by a mix of health care professionals. Common questions to consider when evaluating potential gaps should include:
    a. Shared goals
        i. Are the patient and family goals for critical care routinely incorporated into the care plan?
        ii. Are the patient and family viewed as active members of the team during the establishment of goals?
        iii. Are there clearly articulated and understood goals that are agreed on by all members of the team during the provision of care to all ICU patients and the work of the team in the care of that patient?
        iv. Is progress toward the goals routinely reevaluated in light of the changing course and evolving perspective of the patient and family? Are goals adjusted or refined throughout the dynamic course of the critical care admission as needed?
        v. Are there adequate organizational resources and commitments to permit effective establishment of shared goals in the treatment of ICU patients?
    b. Clear roles
        i. Are each team member's functions, responsibilities, and accountabilities clearly defined? Can each team member articulate and understand the role of the other team members?
        ii. Are the roles and responsibilities of each team member focused on the shared goals of the team and patient?
        iii. Is there clear respect for the contributions of each team member from a nonhierarchical, interdependent perspective?
        iv. Is each team member introduced (and reintroduced) to the patient and family, including a lay description of each member's role and responsibility?
        v. Does each team member go about his or her responsibilities with a reasonable degree of autonomy?
        vi. Is there a clear team leader? Does the leadership role vary according to individual circumstances, problems, or environment?

    vii. Does the team have a reasonable balance between autonomous functions and collaboration?
    viii. Are there adequate organizational resources and commitments for professional development, team education, facilitation of communication, and restructuring of care processes to support the effective division of labor?
c. Mutual trust
    i. Does an environment of mutual trust and support exist among the ICU team? Can breaches of trust be openly discussed and addressed between team members without a detrimental impact on professional or personal relationships?
    ii. Does the hiring process include a focus on the personal and professional values that support an environment of mutual trust? Do members of the ICU team participate in the hiring process across traditional departmental siloes?
    iii. Is the team effective at establishing and maintaining mutual trust with patients and families? Are effective communication skills used to explain the process of establishing goals, sharing information on progress, and incorporating effective negotiation and conflict resolution skills?
    iv. Does the team regularly participate in non–patient care activities (e.g., social interaction) that allow team members to develop greater trust and know each other at many levels?
    v. Is there adequate organizational support of the elements necessary to establish mutual trust among teams?
d. Effective communication
    i. Has the team established a high priority for open, direct, clear, consistent, professional communication between team members?
    ii. Does communication take advantage of all potential modes and technologies of communication for efficiency and convenience?
    iii. Do members of the team use effective listening skills, recognizing that deep listening to the input of all team members, including patients and families, is an essential component of effective communication?
    iv. Are signs of tension and unspoken conflict in the communication process regularly recognized and addressed to improve team communication skills and effectiveness?
    v. Does effective communication occur across the team regardless of traditional hierarchical structures in health care?
    vi. Are the organizational elements for effective communication available to the team?
e. Measurable processes and outcomes
    i. Has the team identified and implemented reliable, timely, and ongoing measures of team performance?
    ii. Are these measures focused on both process/outcomes of care provision and team function or effectiveness?
    iii. Are measures of patient and family satisfaction included in the assessment process?
    iv. Are measures of team member satisfaction included in the team assessment?
    v. Does the team regularly report its measures of success and failure, both internally to the team and to others in the organization?
    vi. Are performance data regularly used for process improvement with respect to both patient care and team function?
    vii. Does the team use any standardized tools to assess team function and quality?
    viii. Are organizational resources and commitment adequate to permit teams to adequately measure quality of patient care and team function?

F. Other Standards
  1. The Joint Commission
    a. Medication management chapter
      i. High-alert, hazardous medication standards
      ii. Look-alike/sound-alike medications
      iii. Monitoring of medication response
      iv. Adverse drug event detection, evaluation, and reporting
      v. Duplicate therapy
    b. National Patient Safety Goals
      i. Two-factor patient identification
      ii. Medication reconciliation
      iii. Safe medication use and labeling
      iv. Anticoagulation management and education
      v. Antimicrobial stewardship program
  2. Centers for Medicare & Medicaid Services (CMS) conditions of participation (42 CFR 482)
    a. Quality assurance and performance improvement programs (§482.21)
      i. Medical errors
      ii. Adverse events
    b. Preparation and administration of medications (§482.23)
    c. Medical records requirements (§482.24)
    d. Pharmaceutical services (§482.25)
      i. Policies and procedures to minimize drug errors
      ii. Adverse drug reaction and medication error detection and reporting
      iii. Drug information standards

VI. TRAINING OF CRITICAL CARE PHARMACISTS

A. Positions and Policy
  1. ACCP position
    a. ACCP clarified its position concerning qualifications of clinical pharmacists providing direct patient care in a 2013 Board of Regents commentary (Pharmacotherapy 2013;33:888-91): Clinical pharmacists providing direct patient care “should possess the education, training, and experience necessary to function effectively, efficiently, and responsibly in this role. Therefore, ACCP believes that clinical pharmacists engaged in direct patient care should be board certified (or board eligible if a Board of Pharmacy Specialties [BPS] certification does not exist in their area of practice) and have established a valid collaborative drug therapy management (CDTM) agreement or have been formally granted clinical privileges by the medical staff or credentialing system within the health care environment in which they practice.”
    b. Board certification
      i. ACCP considers BPS certification the cornerstone of eligibility for direct patient care.
      ii. Eligibility
        (a) Graduate of an accredited school of pharmacy
        (b) Pharmacy licensure
        (c) Postgraduate residency training in area of specialization (i.e., PGY2 pharmacy residency), or PGY1 pharmacy residency and at least 2 years of experience in specialty area with at least 50% of time in the BPS scope of specialty area, or at least 3–4 years of relevant experience with at least 50% of time practicing in the specialty area

      - iii. ACCP has expressed that postgraduate residency training is the preferred training pathway for clinical pharmacists providing direct patient care in previous position statements and a white paper.
  2. ASHP policy
    - a. Policy 2027: "Pharmacists who provide direct patient care should have completed an ASHP-accredited residency or have attained comparable skills through practice experience."
    - b. ASHP has no policy directly related to the provision of direct patient care in a specialty practice area.

B. Potential Workforce Demands
  1. Hospital data
    - a. 6120 hospitals in the United States – 916,752 staffed beds (2024 American Hospital Association survey data; https://www.aha.org/system/files/media/file/2024/01/fast-facts-on-us-hospitals-2024-20240112.pdf)
    - b. According to 2018 AHA survey data, there were 107,276 adult, pediatric, and neonatal ICU beds in community hospitals across the United States (www.aha.org/statistics/fast-facts-us-hospitals).
  2. Critical care pharmacists
    - a. No accurate database to indicate the number of pharmacists spending 50% or more of time in critical care
    - b. Direct patient care by pharmacist provided in 62.2% of ICUs in the United States in 2006. This represents primarily fundamental-level services (Ann Pharmacother 2006;40:612-8). A more recent survey of 1220 institutions revealed 70.8% of ICUs had direct clinical ICU pharmacy services, which is a greater than 13% increase compared with 2006 (Crit Care Explorations 2021;3:1-11).
    - c. A recent survey of 185 critical care pharmacists indicated that the pharmacist/patient ratio is variable, with 84% of respondents caring for more than 15 patients. In addition, 30% of respondents expressed concern about safety relative to workload, and 50% indicated they felt overworked. This survey suggests that ICUs with pharmacist coverage may be understaffed (JACCP 2020;3:68-74).
    - d. A review of ACCP, SCCM, ASHP, and American Pharmacists Association (APhA) membership records identified 2928 individual pharmacists indicating specialization in critical care at the time of the 2012 petition for recognition of critical care as a specialty (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).
    - e. A survey sent to those 2928 pharmacists yielded 504 responses (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).
      - i. Out of the responses, 476 reported that they practiced in critical care (94%).
      - ii. Of those 476, 91% responded that their practice met the definition of critical care pharmacy as a specialty.
      - iii. Among the respondents, 74% indicated they spent at least 50% of their time practicing in the ICU.
      - iv. More than 80% of respondents completed residency or fellowship training in critical care.
    - f. A survey of employers of ICU pharmacists yielded 204 responses (https://www.accp.com/docs/positions/petitions/Final_CRITICAL_CARE_PETITION_For_BPS_Post.pdf).
      - i. Collectively employed 1034 full-time equivalent (FTE) critical care pharmacists
      - ii. Recruited 256 critical care pharmacists during the previous 3 years
      - iii. Estimated a need to hire 234–243 critical care pharmacists in the next 3 years
      - iv. Of the respondents, 99.5% estimated the demand for critical care pharmacists to grow or remain stable at their site during the next 5 years.

- g. Critical Care Societies Collaborative (CCSC) – http://ccsconline.org/workforce
  - i. Collaborative effort of several stakeholder organizations in critical care to define the workforce shortage in critical care and advocate for federal action to address the problem
  - ii. Most of this work has focused on intensivist and ICU nurse shortages, but there is also recognition of shortages of other professionals, including critical care pharmacists.
- h. Current and objective quantification of critical care pharmacist shortage or demand is unavailable.

C. Training Recommendations and Capacity

1. Minimum requirements for all levels of ICU service (levels I–III)
   - a. Graduate of Accreditation Council for Pharmacy Education (ACPE)-accredited school or college of pharmacy
   - b. Licensure and registration by a state board of pharmacy
2. Conventional or preferred postgraduate training (*Pharmacotherapy.* 2011;31(8):135e-175e)
   - a. PGY1 pharmacy practice residency based in a hospital
   - b. PGY2 critical care residency or fellowship
     - i. First critical care pharmacy residency described: 1981 (The Ohio State University)
     - ii. ASHP critical care pharmacy residency standards published in 1990
     - iii. 189 ASHP-accredited critical care residencies in 2024; increased from 8 in 2001 and 39 in 2005
     - iv. Most PGY2 critical care residents are somewhat or very satisfied (91% and 76%, respectively) with their program and mentorship according to a 2012 survey.
     - v. Critical care pharmacy research training: Long history of fellowship training; however, the *ACCP Directory of Residencies, Fellowships, and Graduate Programs* lists fellowship programs with a primary or secondary focus on critical care
3. Nontraditional alternative paths: There is no widely accepted or clearly defined alternative pathway to specialty experience and competence in critical care pharmacy. Some potential pathways and components of a self-directed training program are outlined in the text that follows. The extent and variety of experiences needed may be determined by the practice setting, level of care to be provided, baseline knowledge, availability and willingness of qualified mentors, and other personal and professional skills of the individual. Although many potential paths are defined later, those that provide continued, practical experience during a prolonged period in a supervised or mentored environment are considered of greatest value in developing competency in the ICU setting.
   - a. Mentored or supervised clinical practice experience without residency
     - i. Clinical practice experience must be hands-on and team based under supervision.
     - ii. Mentors may be PGY2- or fellowship-trained critical care pharmacists, clinical pharmacists with equivalent experience, critical care faculty from affiliated schools of pharmacy, intensivist physicians, and/or other critical care professionals.
     - iii. Several mentors may best meet the variety of needs of the mentee pharmacist.
     - iv. Reinforced by frequent reading and analysis of the critical care primary and secondary literature, journal club participation, and frequent critical discussions of the clinical implications of the primary literature
     - v. Normally, expect at least 3–4 years of mentored/supervised experience to gain competency for independent clinical practice (optimal services) in level I and II ICUs. Shorter periods may be adequate to provide lower levels of service to level II and III ICUs.
   - b. PGY1 with supervised/mentored ICU clinical practice experience
     - i. Mentored clinical experiences similar to those described earlier
     - ii. PGY1 with critical care experiences during residency may be adequate to provide fundamental and desirable services to level II and III ICUs.
     - iii. Normally, expect 2–3 years of mentored/supervised experience to gain competency for independent clinical practice (optimal services) in level I and II ICUs.

  c. ASHP critical care traineeship (https://www.ashpfoundation.org/leadership-development/traineeships)
    i. Previously offered through the ASHP Foundation
    ii. Four-month distance education component – Independent reading, web-based education, and teleconference case studies
    iii. Two-week on-site experiential training
    iv. Post-experiential training activities
    v. Is not a comprehensive training program but can be a valuable component of a training program for nontraditional-path clinical pharmacists
  d. Other potential components of a nonconventional training program: Actual program structure will vary depending on the available resources, practice environment, baseline knowledge and skills of the pharmacist, and institutional support.
    i. Graduate degree (e.g., master's degree)
    ii. Continuing education (CE) programming – Live, web based, print
    iii. Attendance at national and regional critical care meetings – CE, networking, research presentations
    iv. Fundamental Critical Care Support course completion (www.sccm.org/Fundamentals)
    v. ACLS, advanced trauma life support (ATLS), and/or pediatric advanced life support (PALS) training and certification
    vi. Regular participation in the SCCM Clinical Pharmacy and Pharmacology Section national journal club
    vii. SCCM Clinical Pharmacy and Pharmacology Section mentor program – Long-distance mentoring program
    viii. Self-arranged experiential rotations at peer institutions under the supervision of a qualified critical care pharmacist
    ix. Visiting professor or scholar programs to bring specialized expertise to the clinical site for on-site experiential training and didactic teaching
    x. Policy, guideline, and protocol development for critical care pharmacotherapy–related issues under the supervision of qualified peers
    xi. Critical care pharmacy service or program development, implementation, and outcome measurement under the supervision of qualified peers

D. Post-training Professional Mentoring and Critical Care Pharmacy Training (Am J Pharm Educ 2013;77:1-7; Am J Pharm Educ 2003;67:1-7)
  1. Mentor-protégé relationship
    a. Symbiotic, nurturing relationship between two adults
    b. Assist each other in meeting shared career objectives
    c. Attributes of a successful mentor-protégé relationship (see Box 1)
    d. Mentor typically 15–20 years older than protégé
  2. Mentor should fulfill five functions:
    a. Teaching – New knowledge, skills, and attitudes
    b. Sponsoring – Helps protégé reach career goals, assists in networking, vouches for abilities, offers protection from threats
    c. Encouraging – Affirming, challenging, inspiring
    d. Counseling – Listening, probing, advising during difficult challenges
    e. Befriending – Acceptance, understanding, and trust

Box 1. Attributes of Successful Mentor-Protégé Relationships

Mentor Qualities
Strong interpersonal skills
Technical competence/expertise
Knowledge of organization and profession
Status/prestige within the organization and profession
Willingness to be responsible for someone else’s growth and development
Ability to share credit
Patience
Protégé Qualities
Self-perceived growth needs
A record of seeking/accepting challenging assignments
Receptivity to feedback and coaching
Willingness to assume responsibility for own growth and development
Ability to perform in more than one skill area
Relationship Qualities
Voluntary
Mutual benefits perceived and derived from the relationship
No conflicts of interest/competition between mentor and protégé
Not confined to professional or business interests

Adapted from: Haines ST. The mentor-protégé relationship. Am J Pharm Educ 2003;67:Article 82, p 2.

3. Phases of the mentor-protégé relationship:
    a. Initiation phase
        i. Weeks to months in duration
        ii. Begin work together
        iii. Mentor coaches protégé, and protégé may provide technical assistance.
    b. Cultivation phase
        i. 2–5 years in duration
        ii. Both individuals realize personal and professional benefits.
        iii. Deeply intimate and personal bonds are formed.
    c. Separation phase
        i. Typically months in duration
        ii. Protégé no longer requires guidance and begins to seek more autonomy.
        iii. Mentor may think they have been deserted, whereas protégé may believe they are being held back.
        iv. Resentment or hostility may lead to end of relationship.
    d. Transformation phase
        i. Years in duration (lifelong)
        ii. Peer relationship evolves.
        iii. Mutual sense of gratitude and appreciation
4. Voluntary versus arranged relationships
    a. Increasingly, organizations are establishing mentoring programs with assigned mentors.
    b. Successful mentoring relationships are voluntary and based on mutual respect.
    c. Successful and powerful people are not necessarily good mentors.
    d. The factors that lead to mentor-protégé relationships are unclear and may be difficult to create through assignment of mentors.

  e. Factors that contribute to successful mentorship:
    i. Common interests
    ii. Common purpose
    iii. Desire on the part of the mentor to participate
    iv. Mentor and protégé must be able to spend time together.
    v. Persistent and regular interaction between mentor and protégé
  f. Formal mentoring programs can be successful, but less so than voluntary relationships.

5. Mentoring and critical care training
  a. Beyond formal residency/fellowship programs, mentor-protégé relationships are essential to the formal development of critical care pharmacists.
  b. Developing critical care pharmacists should seek out mentors with similar interests and purpose who can help them fill gaps in their knowledge, skills, and attitudes relative to critical care practice.
  c. Over time, critical care pharmacists may have several mentor-protégé relationships to meet evolving educational and experiential needs.
  d. Experienced and successful critical care pharmacists should volunteer to mentor junior pharmacists, residents, and students and take their roles as mentors seriously by being kind, helpful, supportive, and encouraging.
  e. SCCM Clinical Pharmacy and Pharmacology Section mentoring services: Practice, education, administration, scholarship

VII. CONTINUING PROFESSIONAL DEVELOPMENT (https://www.acpe-accredit.org/continuing-professional-development/; Resident Survival Guide. Lenexa, KS: ACCP, 2011:123-37; Am J Health Syst Pharm 2004;61:2069-76)

A. General Considerations
  1. Lifelong learning by health care professionals is both a necessity and an obligation to several stakeholders.
  2. CPD is a multifaceted, self-directed, holistic, outcomes-focused approach to lifelong learning.
  3. CPD is a career-long iterative process with continuous cycles, rather than a start and a finish.
  4. Sustained career growth and success are more dependent on CPD than on early career education and training.
  5. CPD should be closely integrated into daily practice and the work environment for success and sustainability.

B. Stakeholders in CPD: Stakeholders may have a role in contributing to lifelong learning, benefiting from the sustained competency of the clinical pharmacist, or both.
  1. Pharmacist-learner (self)
    a. Most at stake
    b. Primarily responsible for developing a self-directed, structured approach to learning and assessment
    c. Must develop an approach that is flexible, integrated, and capable of being sustained throughout decades of practice
    d. Must be prepared to commit personal time to CPD
  2. Employer
    a. Has both an obligation to and an expectation of the clinical pharmacist relative to CPD
    b. Provision of resources
      i. Travel funding (varies depending on institutional budget)
      ii. Access to electronic databases and literature

        iii. Environment that promotes sharing and learning (clinical conferences, journal club, open discussion and debate among colleagues, etc.)
        iv. Protected time to pursue educational opportunities
    c. Establish a credentialing and privileging process that incorporates CPD expectations.
    d. Aligning personal development goals with institutional priorities is mutually beneficial and may increase employer support.
    e. Employer benefits from sustained and expanded competencies of clinical pharmacist and should incorporate into hiring, retention, and promotion decisions
3. Colleagues
    a. Contribute to lifelong learning of the clinical pharmacist
        i. Case-based discussion and debate on daily rounds
        ii. Drug-related questions
        iii. Interdisciplinary teaching rounds
        iv. Clinical conferences, journal clubs
        v. Inclusion in collaborative scholarly activities
    b. Benefit from lifelong learning of the clinical pharmacist
        i. Greater quality and sophistication of contributions to team-based care of critically ill patients
        ii. Educational offerings by the clinical pharmacist
        iii. Collaboration around scholarly activities
        iv. ICU-related treatment guidelines, pathways, and protocols developed by or in collaboration with the clinical pharmacist
4. Students, residents, and fellows
    a. Contribute to lifelong learning of the clinical pharmacist
        i. Assisting in identifying gaps in their own knowledge
        ii. Creating incentive to maintain competency through CPD
        iii. Regularly challenging applicability and relevance of professional knowledge and skills
    b. Benefit from current, relevant knowledge and skills being incorporated into:
        i. Teaching
        ii. Role modeling/coaching and facilitating
        iii. Mentoring
    c. CPD is a lifelong obligation of pharmacists who accept responsibility for training future clinical pharmacists.
    d. The best trainees seek out the most competent teachers, preceptors, and mentors.
5. Patients
    a. Greatest beneficiary of clinical pharmacist CPD
    b. Providing the best possible care to ICU patients should be the biggest motivator for the clinical pharmacist to pursue CPD.
    c. Well-informed patients will seek out the most competent and capable health care professionals.

C. CPD Process: The CPD process is structured around four essential steps. A potential fifth step is documentation of the process, but that should be an integral part of each step, not a separate process.
1. Reflection
    a. Self-assessment process
    b. Evaluation and feedback from others
        i. Coworkers
        ii. Colleagues
        iii. Employer
        iv. Patients
        v. Pharmacy trainees (students/residents/fellows)
        vi. External peer review (e.g., organizational fellowship status; adjunct faculty appointment review)

   c. Personal SWOT (strengths, weaknesses, opportunities, and threats)
      i. Assessment of internal strengths and weaknesses related to knowledge, skills, experiences, and behaviors
      ii. Assessment of external environmental factors for opportunities and threats
      iii. Goal is to identify learning needs and opportunities that exist to address those needs.
   d. Reflection should be both scheduled and episodic.
      i. Annual performance evaluation/self-evaluation (scheduled)
      ii. Some set or chosen anniversary date (scheduled)
      iii. After the care of a complex or difficult patient (episodic)
      iv. After an interaction with a challenging student or resident (episodic)
   e. Result of reflection is to identify two or three specific, well-defined, and achievable learning needs.
2. Plan
   a. Develop a personal development plan (PDP) to address the needs and opportunities identified during reflection.
   b. Includes learning objectives that are specific, measurable, achievable, relevant, and timed (SMART)
   c. Identifies resources needed to address the PDP
   d. Evaluates the availability and access to needed resources and modifies plan accordingly
   e. The PDP should be regularly reassessed and adjusted as needed.
3. Act
   a. Develop an action plan to implement the PDP.
   b. The action plan will need to incorporate a variety of learning strategies and methods (see text that follows).
   c. Incorporating the action plan into the daily practice activities is key to success and sustainability. CPD should not be considered an additional burden.
4. Evaluate
   a. Evaluate the effectiveness of the action plan for achieving the learning objectives of the PDP.
      i. Did the activities provide adequate content, depth, and hands-on experiences to truly address the learning objectives and meet the needs identified during reflection?
      ii. Did the activities stay focused on the learning objectives, and were timelines adhered to adequately?
      iii. Were all competencies adequately addressed?
      iv. How did the CPD activities affect the pharmacist-learner and possibly the patient (often very challenging to measure)?
   b. Evaluation is expected to lead to the next round of reflection and restart the continuous and iterative process of CPD.
5. Portfolio (documentation)
   a. Process of documenting the CPD progression
   b. Although the format may be standardized by employer, regulatory authorities, CE providers, or others, the content should be individualized to reflect the needs, actions, and assessments of the pharmacist-learner.
   c. Is a dynamic, living document that reflects the continuous, iterative nature of CPD
   d. Examples of CPD portfolio formats/templates:
      i. https://www.acpe-accredit.org/pdf/CPD_Portfolio.pdf
      ii. North Carolina CPD Learning Portfolio, North Carolina Board of Pharmacy, https://bpsweb.org/2023/09/29/introduction-to-cpd/
      iii. www.ocpinfo.com/practice-education/qa-program/learning-portfolio/

D. CPD Learning Strategies and Methods
  1. CPE
    a. CPD is not a replacement for CPE, but CPE should be one component of a PDP.
    b. ICU pharmacists should focus on CPE programming that meets their defined educational needs and incorporates several different techniques that will help meet the full range of competencies needed for clinical practice in the ICU.
    c. Accreditation standards maintain minimum quality assurance of CPE activities.
    d. CPE credits are the most widely used "currency" by regulatory bodies, accrediting agencies, and other organizations as a proxy for professional competency, and this is unlikely to change in the near or intermediate term.
    e. Traditional didactic lecture-style CPE activities have several limitations toward achieving CPD learning objectives.
      i. Often non-curricular
      ii. Limited influence on changing practice
      iii. Educational outcomes may not align with the individual's needs.
      iv. Content is sponsor or speaker driven.
      v. Opportunity for bias (or perception of bias), depending on source of support
      vi. CE efforts are often fragmented across professions (not interdisciplinary).
    f. CPE providers are expanding the diversity of educational methodologies and techniques to include interaction, experiential learning, simulation, discussion and debate, and role-playing, among others.
    g. Limited evidence suggests that live CE over print, multimedia format, and a series of programs on a curricular theme is the most effective CE method.
  2. Short courses or seminars
    a. Certificate or credentialing programs
      i. ACLS
      ii. ATLS
      iii. PALS
      iv. Emergency neurological life support (ENLS)
      v. Teaching certificate programs
    b. Structured curricular programs
      i. ACCP Academies
      ii. Fundamental Critical Care Support (FCCS) and Pediatrics Fundamental Critical Care Support (PFCCS) course
      iii. Pharmacotherapy of Neurocritical Care Series (PONS) offered by the NCS
  3. Membership and participation in national organizations
    a. ACCP; Critical Care PRN
    b. SCCM; Clinical Pharmacy and Pharmacology Section
    c. ASHP; Section of Clinical Specialists and Scientists
    d. Several specialty organizations related to critical care (American College of Chest Physicians, American Trauma Society, NCS, American Burn Association, etc.)
  4. Primary and secondary literature
    a. Reading, analyzing, and applying the relevant literature should be central to any strategy of professional development.
    b. No gold standard strategy for staying current with the literature
    c. Many "foraging" strategies will need to be considered and used.

        i. Review table of contents of high-impact journals in critical care (e-mail or rich site summary [RSS] push technology) (e.g., *Critical Care Medicine*, *Intensive Care Medicine*, *Chest*, *American Journal of Respiratory and Critical Care Medicine*, *Journal of Trauma and Acute Care Surgery*, *Journal of Critical Care*).
        ii. Topic alerts (e-mail or RSS) for critical care articles from high-impact multispecialty journals (e.g., *New England Journal of Medicine*, *Annals of Internal Medicine*, *JAMA*, *The BMJ*, *Lancet*)
        iii. Scan high-impact pharmacy specialty journals for critical care articles (e.g., *Pharmacotherapy*, *Annals of Pharmacotherapy*, *American Journal of Health-System Pharmacy*).
        iv. Use of saved search strategies with automatic e-mail alerts on a scheduled interval (e.g., PubMed, PubCrawler, Ovid Medline)
        v. Subscribe to a medical information alert service with high and transparent standards for validity, relevance, and contextual interpretation of the data (e.g., Essential Evidence Plus, FPIN [Family Physicians Inquiries Network] Clinical Inquiries, BMJ Clinical Evidence, Cochrane for Clinicians).
        vi. Scan review journals relevant to critical care (e.g., *Critical Care Clinics*).
        vii. Identify high-quality, relevant, and contemporary clinical practice guidelines for critical care therapeutics (e.g., National Guideline Clearinghouse, PubMed Clinical Queries, MD Consult).
        viii. Use up-to-date systematic reviews (e.g., *Cochrane Database of Systematic Reviews*, *Agency for Healthcare Research and Quality [AHRQ] Evidence-Based Practice Center Evidence-Based Reports*).
        ix. Selective use of other resources (e.g., evidence-based summaries such as Bandolier, Clinical Evidence), critically appraised topics, point-of-care review services (e.g., UpToDate, Medscape), SCCM CPP Section Pharmacotherapy Literature Updates, and meta-search engines (e.g., Trip database)
    d. The tools and resources available for staying current with the literature is a rapidly evolving, dynamic market. The individual pharmacist will need to stay current to maximize use of the literature and will need to adapt his or her strategy over time.
5. Discussion and debate with colleagues, mentors, and other content experts
    a. Therapeutic dilemmas
    b. Complex cases
    c. Primary literature
    d. Guidelines
6. Journal clubs/clinical conferences
7. Interdisciplinary, patient care rounds – Daily interactive discussions of diagnostics, disease states, therapeutics, monitoring, technology in the ICU, ethics, communication with patients and families, etc.
8. Guideline and protocol development for the ICU
    a. Translation of evidence to best practices
    b. Benchmarking with peer institutions
    c. Consensus building
    d. Project management – Implementation and measurement of outcomes
9. Point-of-care learning
    a. Refers to day-to-day learning opportunities
    b. Uncommon disease state or unexpected adverse drug reaction prompts reading and learning.
    c. Complex drug information questions from colleagues

VIII. CORE KNOWLEDGE BASE AREAS FOR PHARMACISTS CARING FOR CRITICALLY ILL PATIENTS (2024 BOARD OF PHARMACY SPECIALTIES CRITICAL CARE CONTENT OUTLINE) (SEE BOX 2)

Box 2. 2024 Board of Pharmacy Specialties Critical Care Content Outline

1	**Critical Care**
1A	**Critical Illness**
1A1	Pathophysiology
1A2	Critical Care Disease States
1A3	Chronic Disease States
1A4	Risk Factors for Critical Illness
1A5	Post-ICU Syndrome (PICS)
1A6	Medical Emergencies
1B	Medical Therapies and Devices
1B1	Mechanical Circulatory Support
1B2	Mechanical/Assisted Ventilation
1B3	Extracorporeal Membrane Oxygenation (ECMO)
1B4	Renal Replacement Therapies
1B5	Lines, Tubes, and Drains
2	**Therapeutics and Patient Management**
2A	**Treatment Planning**
2A1	Diagnosis and Diagnostic Testing
2A2	Pharmacodynamics and Pharmacokinetics
2A3	Goals of Care
2A4	Perioperative Care
2A5	Transitions of Care (e.g., medication reconciliation, disposition, stepdown)
2A6	Medication Delivery (e.g., routes of administration, delivery devices, anatomic alterations)
2A7	Pharmacoeconomics
2A8	Social Determinants of Health
2B	**Pharmacotherapy**
2B1	Pulmonology
2B2	Cardiology
2B3	Nephrology
2B4	Neurology
2B5	Gastroenterology
2B6	Hepatology
2B7	Dermatology
2B8	Immunology
2B9	Endocrinology
2B10	Hematology
2B11	Toxicology
2B12	Infectious Diseases
2B13	Supportive Care
2B14	End-of-Life Care
2B15	Fluids, Electrolytes, and Nutrition
2B16	Trauma and Burns

Box 2. 2024 Board of Pharmacy Specialties Critical Care Content Outline (*con't*)

2	**Therapeutics and Patient Management**
2C	**Treatment Outcomes and Monitoring**
2C1	Therapeutic Targets and Endpoints
2C2	Therapeutic Drug Monitoring
2C3	Physiologic Response Monitoring
2C4	Drug Interactions and Adverse Reactions
2C5	Patient and Caregiver Education and Counseling
3	**Professional Practice**
3A	**Quality of Care**
3A1	Medication Safety (e.g., REMS, VAERS, barcodes)
3A2	Risk Mitigation (e.g., failure mode effects analysis, root cause analysis)
3A3	Healthcare Regulations and Standards (e.g., FDA, TJC, CMS, NIOSH, USP<800>)
3A4	Quality Management/Improvement
3A5	Formulary Management
3A6	Clinical Decision Support Systems
3A7	Development and Justification of Pharmacy Services
3B	Practice Management
3B1	Practice Standards and Guidelines
3B2	Scholarship (e.g., statistics, research methods, literature evaluation, publications)
3B3	Human Subjects Research (e.g., IRB/IEC, compassionate use, right-to-try)
3B4	Interprofessional Healthcare Collaboration
3B5	Pharmacist Preceptorship and Mentorship
3B6	Alternative Healthcare Delivery Modalities (e.g., tele-ICU, post-ICU clinic)
3B7	Disaster Healthcare Management

Information from: Board of Pharmacy Specialties (BPS). Examination Specifications: Critical Care Pharmacy. Available at https://www.bpsweb.org/wp-content/uploads/BCCCP-Examination-Specifications-FALL-2023.pdf.

IX. DISSEMINATION OF CRITICAL CARE KNOWLEDGE

A. Reasons to Disseminate Knowledge
   1. Recognition by peers
   2. Promotion and tenure
   3. Ethical obligation of research
   4. Grantsmanship success
   5. Giving back to the discipline – Critical care pharmacy is a new and evolving specialty.
   6. Travel support

B. Venues for Disseminating Knowledge
   1. Peer-reviewed publications (see text that follows for greater detail)
      a. Traditional, print journals
      b. Open-access (electronic) journals
   2. Non–peer-reviewed publications
      a. Textbook chapter
      b. Pre-print publications
      c. Commentary/editorial
      d. Newsletter

    e. Guideline
    f. Compendia
    g. CE material
    h. Blogs
  3. Abstract (see text that follows for greater detail)
    a. Poster
    b. Platform
    c. Regional, national, international meetings
    d. Virtual poster sessions
  4. Presentation
    a. CE
      i. Live/lecture – Local, regional, national, international venues
      ii. Webinar/podcast
      iii. Recorded/archived
    b. Seminar or conference

C. Publication and Peer-Review Process
  1. Categories of publications (will vary by journal)
    a. Original research
    b. Systematic review (e.g., meta-analysis)
    c. Expert review
    d. Brief reports (e.g., preliminary or pilot data)
    e. Case reports
    f. Practice or educational insights (typically must include assessment of outcomes)
    g. Before-and-after or quasi-experimental studies
  2. Selecting a target journal
    a. Quality and importance of the publication
      i. First-tier journals – Highly important, innovative, and/or high quality
      ii. Second- and third-tier journals – To be considered when paper unlikely to be accepted in, or rejected by, first-tier journal
    b. Target audience and scope of the journal relative to content of publication – Looking for good match on both
    c. Seek input from coauthors, peers, colleagues concerning appropriate journal to target
    d. Publication fees (if applicable)
  3. Preparing the manuscript
    a. Comply with journal requirements.
      i. Historically published with first issue of each volume
      ii. Today, easiest to access online
      iii. Manuscript format
      iv. Margins, font, type size
      v. Abstract format
      vi. Word limits
      vii. Reference style and limits
      viii. Figures and tables
    b. Succinct, focused, non-repetitive – Economy of words
    c. Common weaknesses to avoid (original research) – In manuscript preparation, not underlying research itself
      i. Abstract does not match body of manuscript
      ii. Introduction fails to sell the importance and relevance of the objective(s)

        iii. Poorly worded or unclear study objective(s)
        iv. Methods without results; results without methods
        v. Unnecessary duplication of results in tables and body of manuscript
        vi. Rambling, unfocused discussion
        vii. Failure to adequately address weaknesses of the study (all studies have them)
        viii. Conclusions that reach beyond the data
        ix. Several tables that can be consolidated
        x. Unneeded figures (usually, simplistic presentations of data that can be presented parenthetically)
        xi. Failure to cite the literature correctly or according to journal's requirements
        xii. Exceeding word count limits – Both in abstract and in manuscript
4. Using citation manager software (EndNote, Reference Manager, RefWorks, etc.)
    a. May contain templates consistent with many biomedical journal requirements
    b. Actively cite the literature while writing
    c. Automatically re-sort the references during revisions
    d. Direct download of citations during literature searches
    e. Can include PDF files and your notes in citation file
    f. Develop libraries of commonly used citations
    g. Overall, can ease the writing and formatting process for publication
5. Submitting the manuscript
    a. Greatly simplified by web-based submission
    b. Follow download instructions carefully.
    c. Assessment of writing style and assurance of plagiarism check
    d. Cover letter
        i. Communication to the editor
        ii. Declare category of publication (though now part of submission template).
        iii. Indicate corresponding author (also part of template).
        iv. Some journals encourage a brief explanation of why paper is being submitted to the journal – Relevance, importance, target audience. However, this is declining.
    e. Copyright release
        i. Electronic methods are increasingly used.
        ii. Each author must sign/submit.
        iii. Provide assurance that part or all of content has not been previously published and is not currently under consideration by another publisher. Usually excludes abstracts.
6. Conflicts of interest: All authors must provide conflict-of-interest statements.
7. Review and revision process
    a. Editorial review
        i. The editor or a member of the editorial board may review initially.
        ii. Looking for relevance to journal, general quality of the manuscript, composition, and readability
        iii. Failure to get past the editor's desk results in rejection
    b. Peer or scientific review
        i. Sent to peers with content expertise for review and critique
        ii. Typically, sent to two to five reviewers (varies by journal and internal criteria)
        iii. Most journals request a review to be returned in 10–30 days.
        iv. Reviewers are asked to focus on the quality of the research or content and importance (including relevance to the journal's audience), not copyediting details.

        v. Typical recommendation categories are as follows: Accept, minor revision, major revision, or reject.
        vi. Reviewers provide detailed comments and critique to be shared with the authors, and, often, comments to the editor that are not shared with the authors.
    c. Editor response
        i. The editor (or designee) uses reviewer input to formulate a response to the authors.
        ii. If minor or major revision is requested, details of the required revisions are provided, often including the reviewers' specific comments. The editor often adds requests for revision.
        iii. A timeline for response is included. If manuscript is not resubmitted by deadline, opportunity to publish is usually surrendered.
        iv. A rejection decision is usually final.
    d. Revision process
        i. The authors need to respond to each request. The authors need not agree with each request, but each must be responded to and defended if not revised as advised.
        ii. Common format is a letter to the editor restating each request, with the response to the request immediately following.
        iii. A manuscript incorporating all revisions is submitted with the letter. Some journals request a "track changes" version of the manuscript to ease the rereview process.
        iv. All authors must review the revisions and indicate their agreement with all changes.
        v. Revised manuscripts are often returned to the original peer reviewers for a second review, especially with major revisions. That may result in another round of revision and review.

8. After acceptance
    a. At some point (timelines vary by journal), the corresponding author will receive the galley proof. This is a copyedited, typeset version of the paper that will look like the final publication.
    b. The galley proof will come with comments that must be addressed.
    c. Deadline for galley submission may be as short as 48 hours.
    d. The galley proof must be read very carefully and compared with the manuscript to ensure that copyediting changes do not affect the meaning, tables are formatted as intended, figures and legends are correct, and references are in the correct order and format (there are often errors with references – better with electronic confirmation).
    e. Ideally, all authors should review the galley proof; however, that may not be practical. All authors should approve a review by the corresponding author.
9. Timelines (highly variable by journal)
    a. Important competitive metric for biomedical journals
    b. From submission to response – Can be 2–4 months
    c. Reply to decision – Can be 1 week to 3 months (depends on whether rereview occurs)
    d. Decision to publication – Can be an additional 3–6 months
    e. Sometimes an important consideration when selecting a journal – Manuscript can be tied up for long periods.
    f. Open-access and e-journals have a speed advantage – May have fees.

D. Abstracts and Scientific Presentations
1. Selecting a meeting
    a. Quality and relevance of presentation
    b. Prestige of the meeting relative to authors' career goals
    c. Membership and desire to support an organization

- d. Availability of travel funding
- e. Priorities of key coauthors
- f. Location of the meeting (unfortunate, but true …)
- g. Encore presentations permitted

2. Developing the abstract
    - a. Succinct and effective
        - i. Greatest impact in the least space – No unnecessary words
        - ii. Use of identifiable abbreviations, but not to excess
        - iii. If allowed, use of tables to present results (many disallow)
    - b. Title must be brief, be on point, and capture the reader.
    - c. Clearly stated purpose/objective (minimize introductory material). May need to limit to primary objective.
    - d. Methods and analysis are concise but of adequate detail to permit review.
    - e. Results may need to be limited to the primary end point.
    - f. Conclusion is a single brief sentence directly tied to the objective(s).
    - g. Must meet word or character count limit (tricks and tips depend on organization)
    - h. Revise, revise, revise with input from all authors – Eliminate unnecessary words and content.
    - i. Some organizations may permit students or residents to submit abstracts without data or with partial data.
3. Abstract submission
    - a. Greatly simplified by electronic submission
    - b. Must meet deadline – Most websites shut down after deadline.
    - c. Must carefully follow online instructions
    - d. Pay careful attention to the abstract categories (e.g., clinical practice, original research) to be sure the abstract is submitted under the proper category.
    - e. Word limit usually controlled by software – Difficult to cheat
    - f. If platform presentations are an option, usually need to indicate consideration for platform, if that is the goal
4. Platform versus poster
    - a. Platform slots are intended for presentations that have high-quality content and that are relevant and effective.
    - b. Usually based on reviewer scores
    - c. Many organizations may accept a platform submission as a poster presentation if it was not scored high enough to be accepted as a platform; others may just reject it.
    - d. Authors must be realistic concerning the quality of their abstract when considering submission for a platform, given the meeting, audience, and likely competing research.
5. Review process
    - a. Typically reviewed by three to five reviewers
    - b. Review uses relatively limited scoring criteria, given the brevity of an abstract, combined with a recommendation of accept or reject.
    - c. Reviews are compiled into an overall score, and recommendation is provided to the authors.
    - d. There is no opportunity or time for revision and resubmission. Decisions are final.
    - e. Reviewer comments may or may not be shared with the authors.
    - f. Platform versus poster decisions may also be an outcome of the review process.
    - g. Review process may also be used for determining abstracts to be considered for awards.
6. Poster presentation
    - a. Format (size and/or style) is often specified by the organization.
    - b. Many tips and tricks are available for developing effective posters. Some key issues are:
        - i. Avoid wordy posters – Nobody wants to read them.

            ii. Use tables, figures, and concise bullet lists as much as possible.
            iii. Use a font size that can easily be read from about 5–6 feet (e.g., 24 point or greater).
            iv. Ease of readability is more important than aesthetics – Consider dark letters on a white background.
            v. Use a logical flow from left to right and from the introduction to the conclusions.
            vi. Unless required, do not reprint an abstract on a poster – It is unnecessary and uses valuable space.
            vii. Most institutions have requirements to use logos – Comply with the requirements or potentially run into last-minute challenges with printing.
            viii. Large-print formats have eased the production and transport of posters; however, review proofs carefully for content changes before printing.
            ix. Commercial printers who will ship to the meeting site are a great alternative if last-minute challenges develop.
        c. If there are walk-rounds, be fully prepared to present the key points of your poster in about 5 minutes to allow time for questions. It is important to confirm the time allotment set by each organization because this may vary.
        d. Consider having small, legible versions of the poster at the poster session for those who want a copy to review. In addition, have business cards available.
        e. Plan to have at least one author stay for the duration of the poster session.
        f. Virtual poster sessions are very similar in submission, review, and acceptance process. Presentations are virtual and may involve the abstract only or a more detailed "poster," with interactive sessions scheduled with either random viewers or scheduled peer reviewers.
    7. Platform presentation
        a. Considered an honor of recognition for high-quality, innovative, or impactful work
        b. Presentation is usually limited to 10 minutes, with 5–10 minutes left for questions.
        c. Typical format is a brief slide presentation focused on the most important aspects of the work. Time does not allow a detailed description of all aspects of the project.
        d. May involve peer review/judging if awards are involved
        e. Feedback in verbal or written format is often provided to the presenter.
        f. May also require a poster presentation during one of the poster sessions (varies by organization)
        g. Repeated practice with coauthors, peers, and colleagues, followed by critique and revision, is highly recommended.

E. Participation in the Peer-Review Process (Eos 2011;92:233-40; PLoS Comput Biol 2006;2:e110)
    1. Reasons to participate
        a. Professional obligation
            i. Authors "take" from the process, so they should "give back."
            ii. Contribute expertise to improving the biomedical literature
        b. Professional service to an organization or journal
        c. Recognition, tenure, and promotion – Professional service
        d. Some enjoy reviewing the "raw" product of the biomedical literature.
        e. Educational opportunity for trainees
    2. Reasons to decline invitation to participate
        a. Conflict of interest
            i. Former trainee is author
            ii. Collaborator or coworker is author
            iii. Financial conflict of interest with the subject
        b. Lack of expertise in the subject matter
        c. Lack of time to meet the deadline because of other commitments

3. Getting on the list of potential reviewers
    a. Publishing in the journal
    b. Being recommended by a peer to the editor
    c. Being a recognized expert (nationally, internationally) in a relevant field
    d. Publishing in the field in peer journals
    e. Volunteering through the journal's website or a general call for reviewers – Not an option for all journals
4. Review process
    a. Invitation
        i. Normally sent by e-mail with a response link
        ii. Includes an abstract of the paper and often identifies the authors and institution
        iii. Deadline for submission of review is provided so that reviewer can gauge availability of time.
        iv. Usually a short timeline to respond to invitation
        v. If decline, most journals ask for recommendation of a peer to review (building their reviewer database)
        vi. Once accepted, online access to content is provided (manuscript, review form, instructions to reviewers, etc.).
    b. Tips for the review
        i. Biomedical literature review skills are beyond the scope of this chapter.
        ii. Review is expected to focus on scientific quality and importance of the paper.
        iii. Grammar, sentence structure, and word choices are normally better handled by the copyeditors because of their greater expertise, unless it is critical to the scientific meaning of the paper.
        iv. Connect the dots to find common errors (original research and systematic reviews).
            (a) Objective/purpose and conclusions must match.
            (b) Methods must be directly related to the objective/purpose.
            (c) Methods must be valid, widely accepted, and/or state of the art, including statistical handling of the data.
            (d) Widely accepted guidelines according to study design should be complied with (e.g., CONSORT [randomized controlled trial], STROBE [observational studies], PRISMA [systematic review], STARD [diagnostic accuracy studies]).
            (e) Every method described must have results reported.
            (f) Every result reported has to be tied to a method description.
            (g) Conclusions must be limited to and supported by the study results.
            (h) A fair and complete discussion of study weaknesses must be presented.
    c. Recommendation to editor
        i. Reason for rejection
            (a) Fatal flaw – No amount of rewriting or reanalysis of the data will make it worthy of publication – Poor-quality research or serious errors in methods
            (b) Extent of revision required is so extensive that it is equivalent to starting over
            (c) Valid research that is not important, either because of lack of relevance to the target journal or because manuscript is reporting a well-known finding with no new information
            (d) Republication of all or an extensive portion of the content (may be justifiable [e.g., portions of the methods section when it is a legitimate secondary publication of a previously published study])
            (e) Serious ethical violations
        ii. Revision (minor or major revision)
            (a) Usually for publications believed to have adequate quality and importance, but there are weaknesses that need to be corrected or addressed

            (b) Major revisions usually require a second review – The journal may ask whether you will serve as a continuing reviewer, or it may be assumed.
            (c) Minor revisions may not require rereview; depends on reasons for revision
            (d) Most journals will share the recommendation to the authors, together with the other reviewers' comments to author – Can be very instructive for future reviews
        iii. Accept (without revision)
            (a) Unusual with first submission and review
            (b) Is a truly exceptional manuscript
    d. Submission of the review
        i. Electronic submission according to the journal
        ii. Format is often dictated by the journal.
        iii. Meet the deadline – Delayed reviews prolong the timeline and create workflow challenges for the journal.
        iv. Comments to the authors
            (a) Should be clear, concise, and factual. Should not be abrasive or a personal attack.
            (b) Comments should be clearly referenced to the location in the manuscript (e.g., line number, page/paragraph/sentence).
            (c) Are usually anonymous, but some journals provide option to be identified
            (d) For manuscripts with a fatal flaw, comments can be limited to that flaw.
        v. Comments to the editor
            (a) Should not require extensive comments beyond those to the authors
            (b) Is an opportunity to further explain the rationale for the recommendation or ethical concerns
            (c) Are attributed to the reviewer, but not shared with the authors
        vi. Miscellaneous
            (a) Journal may ask whether you believe an editorial is needed, and a proposed author
            (b) There may be a question about concerns with ethics, animal treatment, or human subjects' protection.

5. Re-review process
    a. Response content
        i. Cover letter detailing response to comments/requests of editor and reviewers
        ii. Revised manuscript (with or without "track changes")
    b. Review process
        i. Should restrict comments to responses in first review. Finding an entirely new set of criticisms to original content is considered "not playing fair."
        ii. Confirm that the revisions have not materially altered the meaning of other parts of the manuscript.
        iii. If the authors have argued not to make a recommended revision, evaluate the validity of the response.
        iv. Recommendations are the same options as for the primary review.
        v. If major revisions are still needed, the editor may decide to reject, or it may undergo another round of reply and review.
        vi. Deadline for the review is often shorter than for the primary review.

Table 1. Critical Care Pharmacy Services in Level 1 Critical Care Centers (Crit Care Med 2020;48:1375-82)

Patient Care

Essential:

- Rounding with interdisciplinary team
- Assists with informed pharmacotherapy decisions
- Provision of drug information to the critical care team
- Provision of drug therapy education to critical care team
- Assists with prevention of inappropriate drug therapy
- Provides clinical consultation for pharmacotherapeutic issues related to critical illness
- Medication consults are available 24 hr/d, 7 d/wk
- Provision of pharmacokinetic monitoring and therapeutic adjustments for targeted drugs
- Review of medication history for determination if maintenance therapy should be continued
- Medication reconciliation services for ICU patients upon admission, transfer, and discharge
- Prospective review of all orders for verification of appropriateness
- Patient and/or caregiver medication therapy education
- Performance of independent patient assessments, e.g., pain/agitation, delirium, nutrition
- Response to cardiac life support by ACLS certified pharmacists 24 hr/d, 7 d/wk
- Response to other resuscitation and time-dependent emergencies in the hospital
- Provision of stewardship of antimicrobials and other selected medications
- Collaboration with other pharmacists within the hospital as needed
- Provision of nutrition therapy plan and modifications in concert with clinical dieticians
- Use of medical record for communication with other healthcare professionals
- Documentation of patient care and economic impact of services
- Documentation of all clinical activities
- Pharmacy liaison with other interdisciplinary team members relative to medication policies, procedures, guidelines, and pathways
- Utilizes pharmacoeconomic analyses to evaluate new critical care pharmacotherapeutic agents
- Proactive in designing, prioritizing, and promoting new clinical pharmacy programs
- Evaluation of clinical pharmacy services for stakeholder satisfaction, significance, and economic value
- Participation in planning preparedness and implementation of processes for disaster and mass casualties
- Majority of time dedicated to critical care services
- Patient care time devoted to care of the critically ill patients
- Decentralized clinical services 24 hr/d
- Development of critical care pharmacist "teams"
- Appropriate pharmacist-to-patient ratio based on patient acuity and complexity

Desirable:

- Provision of medication management problems documentation of progress notes daily
- Preparation and presentation of drug monographs to the P&T Committee
- Provision of telemedicine services if onsite critical care pharmacists are absent

Table 1. Critical Care Pharmacy Services in Level 1 Critical Care Centers (Crit Care Med 2020;48:1375-82) *(cont'd)*

Quality Improvement
Essential: • Medication safety leaders for critically ill patients • Assists with management and reduction of ADEs • Reporting of ADEs to institutional committees and national programs • Evaluation of availability of critical medications through automated dispensing cabinets • Team member in the design process for building new and remodeled critical care areas • Implements and maintains policies and procedures related to safe and effective medication use • Coordination of development and implementation of ICU-focused drug therapy guidelines, order sets, and/or care ICU pathways • Evaluation of impact of ICU-focused drug therapy guidelines, order sets, and/or care ICU pathways • Leads or provides critical care pharmacotherapy to hospital committees • Service on hospital committees • Contribution to hospital newsletter and drug monographs • Identifies and evaluates drug minimization opportunities • Identifies local quality metrics for CQI • Participates in quality assurance programs and gap analysis • Shares responsibility for hospital performance for quality and process measure compliance • Collaborates with other healthcare professions in preparing for accreditation • Assessment of adequacy of pharmacy space and facilities • Implementation of safety technology • Presence of contemporary medication use systems within institution • Presence of contemporary information management systems within institution **Desirable:** • Use of real-time dashboard or analytics monitoring of quality metrics and drug utilization
Research/Scholarship
Essential: • Participates as key investigator for critical care research or case reports • Representation on the IRB as applicable **Desirable:** • Active involvement with critical care pharmacotherapy research • Contributes to the pharmacy and medical literature • Report of research results at professional and scientific meetings • Participates in research design and data analysis • Secures research funding • Collaboration in multicenter research projects • Peer reviewer of the medical literature

Table 1. Critical Care Pharmacy Services in Level 1 Critical Care Centers (Crit Care Med 2020;48:1375-82) *(cont'd)*

Training/Education
Essential: • Provision of training and mentoring of pharmacy students, residents, and fellows • Supports postgraduate residencies and/or fellowship training in critical care pharmacy practice • Evaluation and documentation of trainee outcomes • Provision of education to health professional students and trainees • Development and implementation of training programs for ICU personnel **Desirable:** • Project advisor for pharmacy students, residents, and fellows • Provision of formal education at accredited educational sessions • Active participation in interdisciplinary simulation activities • Certified instructor for certification classes • Identifies and educates medical and community groups relative to pharmacist role on healthcare team
Professional Development
Essential: • Maintains master of critical care pharmacotherapy knowledge • Maintains certification in life-support courses • Seeks board certification when eligible • Involvement in nonpatient care activities • Provision of formal accredited educational sessions • Membership in critical care and pharmacy organizations • Availability of protected time for education, administrative, and research/scholarship activities • Mechanisms in place for career development

ACLS = advanced cardiac life support; ADE = adverse drug events; CQI = continuous quality improvement; ICU = intensive care unit; IRB = institutional review board; P&T = pharmacy and therapeutics.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: A**

The journal Drug Intelligence and Clinical Pharmacy (now Annals of Pharmacotherapy) was the first to publish a critical care therapeutics column in 1982, which was a landmark event relative to the evolution of critical care pharmacy (Answer A). Although the other journals listed—Pharmacotherapy (Answer B), Chest (Answer C), and Heart and Lung (Answer D)—publish critical care therapeutics articles, Annals of Pharmacotherapy was the first to incorporate a critical care therapeutics column into its publication.

2. **Answer: C**

In 2001, ACCM, which exists within the organizational framework of SCCM, formed the two task forces focused on models of critical care delivery, the definition of an intensivist, and the practice of critical care medicine within three different proposed models (Answer C). Neither the Institute of Medicine (Answer A) nor ACCP (Answer B) was involved in formulating the levels of critical care delivery. Although the Clinical Pharmacy and Pharmacology Section of SCCM (Answer D) may have contributed to this document, it is not mentioned in the publication.

3. **Answer: D**

In a 2009 study by MacClaren and Bond, mortality increased in thromboembolic and infarction-related events in ICU patients without clinical pharmacy services compared with ICU patients with clinical pharmacy services: 37%, $p<0.0001$ (Answer D). Although the impact of clinical pharmacists in affecting QTc-interval prolongation (Answer A), preventable adverse drug interactions (Answer B), and drug-drug interactions (Answer C) has been evaluated, differences in mortality have not been documented. Therefore, these answers are incorrect.

4. **Answer: A**

The core knowledge areas for pharmacists caring for critically ill patients include pulmonary, cardiology, psychiatry, oncology, neuroscience, nephrology, hepatology, nutrition, gastroenterology, surgery, trauma, burn, pharmacology, transplantation, supportive care, medical emergencies, immunology, endocrinology, hematology, nephrology, toxicology, and surgery. Therefore, nephrology (Answer A) is correct. Dermatology (Answer B), rheumatology (Answer C), and obstetrics (Answer D) are not considered core knowledge areas and are therefore incorrect.

5. **Answer: C**

The landmark study documenting a decrease in preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds was published in the Journal of the American Medical Association by Dr. Lucian Leape and colleagues (Answer C). This highly publicized article published in a mainstream medical journal by a physician remains one of the foundational studies documenting the association of critical care pharmacy services with favorable health care outcomes. The other mainstream medical journals listed, New England Journal of Medicine (Answer A), Lancet (Answer B), and Annals of Internal Medicine (Answer D), have not published similar articles on preventable adverse drug reactions after the inclusion of pharmacists on interdisciplinary medical rounds.

6. **Answer: B**

As stated, there were eight ASHP-accredited critical care pharmacy residencies in 2001. In 2021, ASHP notes 168 ASHP-accredited critical care pharmacy residencies. Assuming linear growth, the 160-residency increase over 20 years equals an increase of eight residencies per year (Answer B is correct). Although this represents significant growth, more than 2200 pharmacists would be needed to provide critical care pharmacy services, assuming 30 patients/pharmacists in the more than 67,000 adult ICU beds in the United States as of 2009. Answer A (5 residencies/year), Answer C (12 residencies/year), and Answer D (15 residencies/year) are incorrect.

7. **Answer: C**

The preferred and recommended pathway to training in critical care pharmacy is a PGY1 pharmacy practice residency, followed by a PGY2 critical care residency. This is especially true for the provision of desirable-to-optimal pharmacy services in ICUs providing level I and II services. Critical care fellowship training is an option that would also be considered preferred; however, the intent is for a greater research and academic focus. The demands of the workplace often exceed the supply of PGY2-trained critical care pharmacists. And although many of the alternative pathways available to gaining experience, knowledge, and skills in critical care pharmacy have been successful, these are not considered preferred pathways, given the high degree of variability and inconsistency of resources to support them, therefore options A, B and D are non-preferred alternative pathways and are incorrect.

8. **Answer: C**

Even though the principles of team-based health care are all interdependent, effective communication is most tightly linked to mutual trust. Open and frank communication and the willingness to state your beliefs and challenge those of your teammates require a high level of mutual trust to keep the relationship and conversation professional and nonpersonal. Without mutual trust, communication can be more guarded, ineffective, and political. Options A, B and D are relevant principles of team-based healthcare, but not as tightly linked to effective communication, and are incorrect.

9. **Answer: B**

Although structured mentor-mentee programs can be successful, there is a greater probability of success with relationships that are voluntary and that evolve from mutual interests and a perceived opportunity to have a mutually beneficial relationship. Mentors must be willing to serve in this role, which can require a great deal of time and effort; they wish to work with mentees who are highly motivated with a track record of accepting challenges. Moreover, mentees must be responsive to feedback and teaching. Mentees seek out mentors with shared interests, a record of sharing their time and expertise, and the necessary prestige and position in the organization to promote and create opportunities for them. In an arranged relationship, it is less likely that all of these factors will come together to lead to a highly productive relationship. Mentoring relationships can exist both within and outside formal training programs like residencies and fellowships so option A is incorrect, and clinical pharmacists will often have several mentors through the different stages of their career to address different and evolving needs as they mature in their practice and scholarly activities so option D is incorrect. Finally, although mentored training programs are a viable option for the nonconventional training of critical care pharmacists, they are not an exclusive pathway so option C is incorrect.

10. **Answer: D**

Continuing pharmacy education should be included as an important strategy in a CPD PDP, and therefore options A and B are incorrect. The self-directed learner should select CPE programs that are relevant to their PDP, incorporate active learning strategies, are preferably curricular based, and are free of commercial or other bias. Continuing professional development is not an alternative to CPE; rather, it is an individualized, self-directed, continuous, and iterative process intended to address specific learning objectives developed over time by the pharmacist-learner. Continuing pharmacy education is an important component of this process, but it should not be the only learning strategy. Both CPD and CPE can include multiple learning strategies, so option C is incorrect.

11. **Answer: C**

The recently published Standards of Practice for Clinical Pharmacy, which includes a standardized process of care endorsed by all major pharmacy practitioner organizations, is intended to be applicable to any practice environment, regardless of acuity or complexity. Like other professions (e.g., medicine, nursing, physical therapy), clinical pharmacy must define and apply standards of care to create consistent expectations by all stakeholders. It is often argued that clinical pharmacists in different complex or unique practice environments cannot possibly conform to a standard of care; however, a thoughtful review of the Standards of Practice for Clinical Pharmacy reveals that it can be easily incorporated into any practice environment, and therefore options A, B and D are incorrect.

12. **Answer: A**

Clinical pharmacists practicing in the ICU have long had a broad educational role that includes students and residents in their own profession, residents and students in other professions, and colleagues on the critical care team, as well as coworkers in the pharmacy department, among the target audiences. Clinical pharmacists have used many different strategies and techniques to teach these diverse audiences across different learning environments. Although there are exceptions, the frequent or regular inclusion of patients and families in their educational activities is a more recent development. Many factors have led to this change, including a greater focus on patient- and family-centered care, greater inclusion of patients and families as members of the team, increased demand for inclusion by patients and families, inclusion of patient satisfaction scores in pay-for-performance metrics (including pain control and understanding of medications), and greater patient awareness and interaction in the ICU with changes in sedation goals. It is anticipated that clinical pharmacists in the ICU will increasingly be directly involved in patient and family discussions and education. Options B, C and D all represent traditional audiences for clinical pharmacist educational efforts and are therefore incorrect.

13. **Answer: B**

In the context of CPD, episodic opportunities for reflection refer to spontaneous, unscheduled events that contribute to the self-assessment of learning and training needs that can be incorporated into the overall PDP. Scheduled reflection usually involves a predictable cycle like performance evaluations, annual self-evaluations, peer feedback as part of annual assessment, or a decision to schedule reflection around some set anniversary (e.g., hire dates, birthdays, end of academic year), and therefore options A, C and D are incorrect. Examples of opportunity for episodic reflection may include the challenges of managing a very difficult case, post-event debriefings for code responses, experiences with a difficult student or resident, or a request to develop a treatment guideline that is outside the clinician's usual area of expertise.

14. **Answer: B**

A methodological flaw that results in the collection and reporting of incorrect data would be considered a "fatal flaw" that no amount of rewriting or reanalysis could correct. Poor writing can be corrected with revision by the authors or during copyediting, but if the study is well conducted and has value, this would not necessarily be a reason to recommend rejection so option A is incorrect. Disagreements concerning statistical analysis are not uncommon; however, the authors may have a valid explanation or be able to revise the statistical analysis if it is not a major departure from the original intent of the study meaning option C is incorrect. It is also not uncommon for the abstract to disagree in some way with the body of the manuscript, and there is an opportunity to correct that during revisions so option D is also incorrect.

RESEARCH DESIGN, BIOSTATISTICS, AND LITERATURE EVALUATION

JULIE E. FARRAR, PHARM.D., BCCCP

UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER
MEMPHIS, TENNESSEE

DAVID M. HILL, PHARM.D., MS, FCCP, FCCM, BCPS, BCCCP

REGIONAL ONE HEALTH
MEMPHIS, TENNESSEE

RESEARCH DESIGN, BIOSTATISTICS, AND LITERATURE EVALUATION

JULIE E. FARRAR, PHARM.D., BCCCP

UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER
MEMPHIS, TENNESSEE

DAVID M. HILL, PHARM.D., MS, FCCP, FCCM, BCPS, BCCCP

REGIONAL ONE HEALTH
MEMPHIS, TENNESSEE

Learning Objectives

1. Identify factors influencing the conduct of essential critical care research.
2. Evaluate the appropriateness of various statistical tests for a set of data.
3. Apply concepts of research design and analysis to clinical care.

Abbreviations in This Chapter

4F-PCC	Four-factor prothrombin complex concentrate
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
CI	Confidence interval
CRP	C-reactive protein
ICU	Intensive care unit
IRB	Institutional review board
NMBA	Neuromuscular blocking agent
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
QI	Quality improvement
RR	Relative risk
RRR	Relative risk reduction

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Investigators are planning a clinical trial to determine the optimal resuscitation fluid for trauma patients. This study will seek to determine whether administering crystalloid fluid, such as lactated Ringer solution, or a transfusion strategy involving packed red blood cells in the trauma field improves survival to hospital discharge. The investigator team has consulted with various ethics scholars to identify relevant issues to be addressed in the trial design. Which issue is most relevant to the ethical conduct of this study?
   A. Treatment blinding.
   B. Uninformative or niche study population.
   C. Consent obtained from injured subjects.
   D. Design as a noninferiority trial.

2. The investigators of a new study are seeking to identify the optimal end point and study population to test the effectiveness of a novel drug compound for septic shock. The novel drug compound is a recombinant protein that mediates the inflammatory cascade of sepsis and has had impressive results for all etiologies of septic shock in preclinical animal studies. Historical estimates of septic shock mortality are 35%–40% in previous studies from the past 10 years; this guides the investigators to calculate a required sample size of ~800 patients to achieve 80% power. A more recent study of septic shock reported 28-day mortality to be 20% in the standard treatment arm. Which best describes the rationale for selecting a study population or primary end point?
   A. The study should limit inclusion to patients without a high level of comorbid conditions at baseline to limit confounders.
   B. The study should expand the target population to include patients with sepsis, not just septic shock, to show a 28-day mortality benefit.
   C. The sample size of the new study will need to be larger than earlier studies to increase likelihood of obtaining power.
   D. The study should limit study inclusion to patients with septic shock caused by pneumonia to test a relevant study population.

3. A quality improvement (QI) initiative is implemented to improve antimicrobial dosing for patients with septic shock presenting to the emergency department. As the pharmacy representative, you have worked with the pharmacy operations team to ensure that an appropriate selection of antimicrobial agents and doses is available in the automated drug-dispensing machines. Which factor will be most important in showing the effectiveness of this QI initiative?
   A. Obtaining informed consent for participation in the QI initiative.
   B. Identifying patients with septic shock in triage.
   C. Creating a community advertising campaign to bring awareness to the initiative.
   D. Determining the social value of the QI initiative.

4. An epidemiologic study seeks to determine the impact of adverse drug events in the intensive care unit (ICU) on patient outcomes, which have an estimated incidence of 52%. Which would be the best approach to conducting this study?
   A. Randomized controlled trial with a test for continuous variables to determine the difference in outcomes.
   B. Retrospective case-control study with a test for proportions to determine the difference in outcomes.
   C. Prospective observational study with survival analysis to determine the difference between cohorts.
   D. Retrospective cohort study with a test for proportions to determine the difference in outcomes.

5. A case-control study is conducted to determine whether proton pump inhibitor (PPI) use is associated with an increased risk of developing *Clostridioides difficile* infection (CDI). The final analysis shows the odds ratio (OR) for CDI with PPI exposure to be 1.3 (95% confidence interval [CI], 0.8–1.5). Which best describes the results?
   A. PPI exposure increases the risk of CDI by 130%.
   B. PPI exposure reduces the risk of CDI by 20%.
   C. PPI exposure increases the risk of CDI by 30%.
   D. PPI exposure is not associated with an increased risk of CDI.

6. A systematic review evaluated the effect of albumin for fluid resuscitation. A meta-analysis that evaluated the effect of albumin use compared with normal saline on 28-day mortality reported a combined OR of 0.45 (95% CI, 0.3–0.75) for the treatment of hypovolemic shock caused by trauma. For the treatment of septic shock, albumin compared with normal saline resulted in a combined OR of 1.1 (95% CI, 0.98–1.21) when evaluating 28-day mortality. Which best represents the findings of the review?
   A. Albumin increased mortality in trauma but did not affect survival in the treatment of septic shock.
   B. Albumin increased survival in trauma but did not affect survival in the treatment of septic shock.
   C. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma but improved survival in the treatment of septic shock.
   D. Albumin did not affect survival in the treatment of hypovolemic shock caused by trauma or septic shock.

7. A critical care pharmacist is faced with an acute drug shortage in which no furosemide is available for immediate use in patient care. During patient care rounds in the ICU, the decision is made to implement a fluid-conservative strategy for a patient with acute respiratory distress syndrome (ARDS). The critical care pharmacist procures an allotment of bumetanide. Which statement best describes the course of action for this patient?
   A. The pharmacist uses an understanding of the medical literature and experiential knowledge to develop a titration scheme using bumetanide to achieve a central venous pressure of less than 4 mm Hg.
   B. The pharmacist uses an understanding of research trial design and experiential knowledge to develop a titration scheme using bumetanide to achieve a central venous pressure of less than 4 mm Hg.
   C. The pharmacist uses a friendly rapport to convince the nephrologist to treat this patient with hemodialysis to achieve a goal central venous pressure of less than 4 mm Hg.
   D. The pharmacist uses an understanding of research ethics to obtain informed consent from the patient's surrogate for treatment with bumetanide.

8. In a study of ARDS, patients are treated with a neuromuscular blocking agent (NMBA) or placebo to determine whether administering a NMBA within the first 48 hours of presentation improves 28- and 90-day survival. The study enrolled an unequal distribution of patients, with more patients having severe ARDS than moderate and mild ARDS. The post hoc analysis of the results showed a survival benefit with NMBA administration for the patients with severe ARDS. Which rationale best describes why NMBAs should not be administered to patients with mild to moderate ARDS?

   A. Patients with mild ARDS have a lower mortality rate and are therefore less likely to benefit from the test treatment.
   B. Patients with mild and moderate ARDS are inherently different from patients with severe ARDS because of their etiology and presentation.
   C. NMBAs are periodically on shortage from the manufacturer and need to be prioritized for necessary medical indications.
   D. The end points selected do not carry sufficient social value to warrant treatment.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 3: Professional Practice
    a. Task B: 1–3

I. INTRODUCTION

A. Epidemiology of Critical Care in the United States – Why continued research is essential to improving the delivery of care to patients
  1. 10.1%–28.5% of all hospital inpatients receive care in an intensive care unit (ICU), approximating 5.7 million adults. Estimated mortality for ICU care is 20%–40% for common critical care syndromes (Crit Care Med 2012;40:1072-9).
  2. 16.9%–38.4% of total hospital costs are spent on critical care services, approximating $121–$263 billion.
    a. 5.2%–11.2% of national health care expenditures
    b. 1% of gross domestic product

B. Why Pharmacists Need to Understand the Fundamentals of Research Practice, Trial Design, and Literature Evaluation – High rates of morbidity and mortality necessitate efficient and efficacious decision-making on the part of caregivers.

C. Necessity of Clinical Research in Critical Care – To optimize patient outcomes and minimize potential patient harm while providing efficient stewardship of finite resources

D. Synthesizing Medical Knowledge with Experiential Knowledge and Pathophysiologic Reasoning – Essential to creating patient-specific therapy care plans

II. BIOETHICS

A. The Belmont Report – Originally created as a result of the National Research Act of 1974; outlines the fundamental ethical principles for the conduct of clinical research
  1. Respect for individuals dictates that each research participant be treated with respect for his or her dignity and autonomy. As such, informed consent shall be obtained from research participants or their surrogates.
  2. The principle of justice requires that investigators recruit research subjects in a manner that allows equal access to participation for all populations that may potentially benefit from the research endeavor.
  3. Beneficence requires research investigators to ensure that risks are minimized and benefits maximized for research participants.

B. A framework for the ethical conduct of clinical research includes seven requirements: (1) social value, (2) scientific validity, (3) fair selection of research participants, (4) favorable risk-benefit ratio, (5) independent review, (6) informed consent, and (7) respect for enrolled participants (JAMA 2000;283:2701-11).

C. Equipoise – Must be present for the conduct of a clinical trial. Equipoise is defined as the state of uncertainty between treatments A and B for a given population of subjects with a predefined disease and/or syndrome. Once the balance of uncertainty between treatments A and B is disturbed such that one treatment is believed to be superior, the risk-benefit ratio is altered such that treatment may not be beneficial to the individual research subject. Example: a proposal for clinical research ethics in critically ill patients during pandemics (*Front Public Health.* 2024;12:1359654.)

D. The Common Rule – Created in 1991 as uniform ethical standards for research after a series of exposures of unethical research misconduct, such as the Tuskegee syphilis study. This rule defined human participant research, developed the process of informed consent, and established the requirement of institutional review boards (IRBs) (JAMA 2017;317:1521-2).
   1. The Common Rule has undergone major changes, with most implementation occurring in 2019 (Chest 2019;155:272-8). These included the following:
      a. New categories and definitions of exempt or excluded research studies
      b. Allowance of a single IRB for multi-institutional studies
      c. Exclusion of public health surveillance as research
      d. Requirement of concise, focused consent forms and online posting of consent as applicable
      e. Allowance of broad consent for identifiable biospecimens in future unspecified research studies

III. PRACTICAL CHALLENGES TO CRITICAL CARE RESEARCH

A. Institutional Review Board (IRB)
   1. IRB of record versus institutional versus independent versus relying IRB
   2. Important considerations for a priori planning
      a. Differences: Processes, time, cost, forms, etc.
      b. Central IRB

B. Research Subject Recruitment – To maximize external validity, research subjects recruited for participation in a clinical trial should be representative of the general population of patients with the disease or syndrome.
   1. Critical care is exemplified by the provision of supportive care for the treatment of diseases and syndromes.
      a. Diseases are characterized by the specific test used to identify the pathophysiologic process.
      b. Syndromes are often identified by the presence of a constellation of signs and symptoms that suggest the presence of a disease that exists across a spectrum of severity.
   2. Recognizing the attendant syndrome is critical for the timely provision of therapy and, in research, subject recruitment.
      a. Heterogeneity in syndromes challenges the ability to identify subjects with similar severity or probability for similar clinical outcomes for participation in clinical research.
      b. In addition, heterogeneity challenges the ability to interpret the results from dissimilar populations, even though they may have a single syndrome in common.
      c. Discrepancies between results from basic and early clinical studies versus adequately powered controlled trials show that surrogate outcome measures (e.g., organ function) or biomarkers may not reliably predict clinical benefit (Am J Respir Crit Care Med 2015;191:1367-73).
   3. Unique to critical care clinical research is the need to enroll subjects similar in acuity or at a similar stage in the process of their syndrome to allow meaningful comparisons.
   4. Use of non-standardized definitions and lack of power complicate data synthesis and meta-analysis (Am J Respir Crit Care Med 2014;189:1469-78).
   5. Selection of end points should be based, in part, on the ethical values outlined previously. End points should provide social value and have scientific validity. A growing area of emphasis in research is on the need to design patient-centered studies (JAMA 2012;307:1583-4). (Example: Positive vs. negative neurological outcome, rather than mean change in modified Rankin Score.)

C. Informed Consent
   1. Necessity depends on many factors (e.g., IRB or trial design)
   2. 6th–8th grade literacy level
   3. Because of the acute nature of critical illness, it may be singularly difficult to obtain informed consent within a short time.
   4. Obtaining informed consent is particularly challenging for critically ill patients, primarily because many critically ill patients lack decisional capacity because of the acute nature of their illness and/or the effect of medications.
   5. Research that involves subjects with impaired consent within the ICU should include plans for assessment of capacity. The University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) is a 10-item scale that assesses capacity for enrollment into clinical research (Arch Gen Psychiatry 2007;64:966-74).
   6. Surrogates and family members are recognized as having authority to provide consent on the behalf of patients, often termed "legally authorized representative," despite the ambiguous legal standing on this issue in several states.
      a. It is important to realize that underlying motives for proxy consent may include the belief that participating in the research protocol will lead to improved care.
      b. Important to acknowledge that patients and surrogates entrust clinical researchers to act in their best interests
      c. Research supports that surrogate consent and patient preferences agree most of the time, but discrepancies may occur in studies considered higher risk (Chest 2001;119:603-12; Crit Care Med 2012;40:2590-4).
   7. One area of growing utilization is digital consent (even video consent). Digitalized consent has the ability to increase comprehension, particularly in those with poor literacy or a lower socioeconomic status (JAMA Cardiol 2020;5:845-7; JAMA 2015;313:463-4; EPMA J 2018;9:225-34).

D. Waiver of Informed Consent
   1. In select circumstances, informed consent may be waived by the IRB.
   2. Of note, differences exist in the guidance between the Department of Health and Human Services and the U.S. Food and Drug Administration (FDA) for waiver of informed consent. In many circumstances, local IRBs will follow the Common Rule as the minimum standard. Further, restrictions regarding the use of a waiver of informed consent vary by country and culture (Theor Med Bioeth 2016;37:441-6).
   3. Waiver of informed consent is typically granted for any of the following circumstances:
      a. Research that is deemed of minimal risk to the participant, does not adversely affect the welfare of the subject, and could not otherwise be practicably carried out
      b. Research that is carried out to evaluate public benefits or service programs
      c. Research in emergencies when consent is not possible, delays lifesaving intervention, or involves standard-of-care therapy.
         i. An example is a study testing the hypothesis of whether drug A is noninferior to drug B for status epilepticus (N Engl J Med 2012;366:591-600).
         ii. A trial conducted in France that investigated the timing of initiation of renal replacement therapy did not require written informed consent because the standard of care was included in both treatment arms (N Engl J Med 2016;375:122-33).
   4. Controversy exists regarding waiver of consent for quality improvement (QI) research. Currently, QI research is subject to the interpretation of local IRBs, as mentioned previously (N Engl J Med 2015;372:855-62).
      a. Keystone ICU project was a joint collaboration between investigators at Johns Hopkins University and the state of Michigan to reduce central line -associated bloodstream infections in ICU patients using a checklist (N Engl J Med 2006;355:2725-32).

        i. Study was classified as exempt from IRB review and informed consent because of the study's QI nature.
        ii. After a complaint, the Office for Human Research Protections of the Department of Health and Human Services originally faulted the investigators for not obtaining informed consent. Subsequently, the Office for Human Research Protections reversed course and classified the project as a "non-research" activity.
    b. Inconsistent interpretation by local IRBs, in the absence of clear guidance from the Office for Human Research Protections, contributes to confusion regarding the necessity of informed consent in QI initiatives (Jt Comm J Qual Patient Saf 2008;34:349-53).

E. Community Consent
  1. Occasionally, critical care research will need to be conducted in the general community. Obtaining consent in this scenario would be impossible, given the medical condition of the research subject. Example: intramuscular therapy compared with intravenous therapy for prehospital status epilepticus (N Engl J Med 2012;366:591-600). In this study of prehospital emergency care, informed consent would be impossible to obtain in the field. Therefore, IRBs engaged local community consultation, according to regulations, and provided approval.
  2. Guidance exists for investigators to inform the community and community leaders before undertaking the research endeavor.
  3. Approval for this type of research is required from local IRBs.
  4. This type of approval falls under Exception from Informed Consent
    a. Not to be confused with Waiver of Informed Consent (Prehosp Disaster Med 2019;34:111-3)
    b. Consider the affected community (e.g., culture, vulnerabilities, etc.) (Prehosp Disaster Med 2018;33:457-8)

F. Social Determinants of Health
  1. The conditions in which people are born, grow, live, work, and age
    a. Education level/income/occupation/recreational opportunities
    b. Physical environment (e.g., housing, utilities availability, neighborhood, safe drinking water, clean air, transportation, etc.)
    c. Gender inequity
    d. Racial segregation
    e. Food insecurity/nutritious choices
    f. Early childhood experiences/development
    g. Crime or violent behavior exposure
  2. Money, power, resources
    a. Global, national, local stratifications and inequities
    b. Complex interplay (poor health/education↔employment↔income↔healthcare/nutrition↔stress↔ substance abuse/unhealthy habits)
  3. May have a higher impact on health than healthcare

Practice Case

1. You are working with a multicenter group to develop a cluster-crossover randomized trial. Patients will be recruited at 12 large academic medical centers in eight metropolitan cities. The study will involve a comparison of intravenous haloperidol with intravenous droperidol for acute agitation in the emergency department. Which of the following would NOT qualify as an essential practical consideration for this proposed study design?
   A. Informed consent - unclear whether waiver of informed consent would be appropriate because both agents may be considered current standard of care or whether community consent might be more appropriate.
   B. Social determinants of health - are some patients more likely to be enrolled in study depending on local perceptions of etiologies of agitation (e.g., drug use, psychological disorders)
   C. Subject recruitment - important to ensure that homogeneous populations are enrolled despite institutional and geographic differences that could significantly affect results.
   D. Blinding - unnecessary bias is introduced into the study due to the inability to blind patients and providers to drug selection.

IV. STUDY DESIGN (FIGURES 1 AND 2)

A. Randomized Controlled Trial
   1. Hallmark of clinical research. Study design seeks to minimize bias through randomization of subjects, blinding of investigators and all participants, and analytic approach. This should leave at least two groups that differ only in study treatments.
   2. Experimental design to test the effects of an intervention compared with either placebo or the established standard of care (treatment or process of care); allows for description and causality

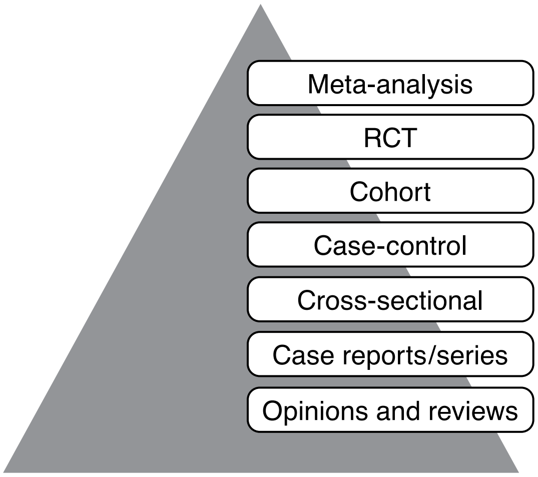
Meta-analysis
RCT
Cohort
Case-control
Cross-sectional
Case reports/series
Opinions and reviews

Figure 1. Hierarchy of clinical evidence.

RCT = randomized controlled trial.

Sevransky JE, Checkley W, Martin GS. Critical care trial design and interpretation: a primer. Crit Care Med 2010;38:1882-9.

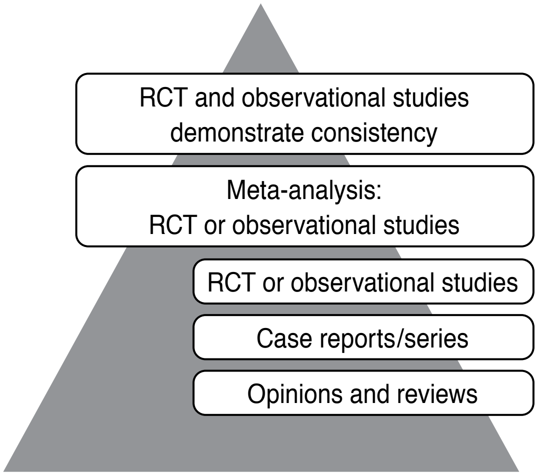
RCT and observational studies demonstrate consistency
Meta-analysis: RCT or observational studies
RCT or observational studies
Case reports/series
Opinions and reviews

Figure 2. Proposed revision to hierarchy of clinical evidence.

Gershon AS, Jafarzadeh S, Wilson KC, et al. Clinical knowledge from observational studies. Am J Respir Crit Care Med 2018;198:859-67.

3. Preliminary research should exist to suggest that the intervention is based on pathophysiology and repeated outcomes consistent with the existing scientific understanding sufficient to warrant the proposed testing on patients.
4. While historically considered the gold standard for research, many limitations exist to the application and interpretation of randomized controlled trials in the ICU (Front Immunol. 2018;9:1502).
    a. Heterogeneous population: The assumption that all patients would benefit from a treatment is unlikely.
    b. Gaps in understanding: Prognostic markers and definitions are often limited, raising concern for inappropriate inclusion and/or exclusion.
    c. Therapeutic optimization often unknown: Preclinical data is often highly different from the population studied (healthy humans or rodent models) limiting confidence in extrapolation.
    d. Clinical equipoise: Uncertainty surrounding the intervention in question may be subjective, and opinions on what would be considered the standard of care may differ at local, national, and international levels in the critically ill. An ethical approach to the comparator arm must therefore be carefully considered (Circulation 2007;115:1164-9).
5. Trial enrichment is a mechanism in which a specific subgroup of a population who have higher likelihood of a response to an intervention are selected over those who may not (Nat Rev Nephrol 2020;16:20-31).
    a. Prognostic enrichment selects for patients with a higher likelihood of disease-related interest (i.e., mortality)
    b. Predictive enrichment selects for those patients who are more likely to respond to a treatment based on underlying biologic mechanisms or physiology (i.e., inflammatory markers in ARDS)

B. Observational
1. Observation of clinical practice; no intervention is tested
2. Describes associations between phenomena
3. Case-control study
    a. Includes patients who did and did not experience an outcome of interest
    b. Hypothesis generating and retrospective design
    c. Provides cost-effective means to determine the association between the risk factor and the outcome of interest
    d. The case group that experienced the outcome are compared with the control group that did not experience the outcome to identify the differences and risk factors (i.e., exposures) for developing the outcome of interest.
    e. Potential for selection bias and confounding because study begins with the "effect" (subjects selected based on outcome of interest) in order to identify a potential causal association (of note, it is not possible to definitively determine causation from a single observational study)
    f. Cases and controls are representative of the population with the disease and should be chosen in a way to minimize selection bias. Controls are randomly selected out of the same population from which the cases arose.
4. Cohort study
    a. Includes patients who did and did not experience an exposure of interest. May be prospective or retrospective in design
    b. Observational study of a given population over a given time to determine the relationship between exposure and outcome of interest
    c. Describes the natural progression of a disease or syndrome
5. Case reports/case series
    a. Describes the experience in treating a single patient or the cumulative experience in treating a series of patients

    b. Typically novel or rare patient population or intervention
6. Challenges with observational studies
    a. Missing data are frequently a problem within observational research and may be classified as missing completely at random, missing at random, or missing not at random (Am J Epidemiol 2012;175:210-7).
        i. Missing completely at random data are truly random and case-dependent and are at decreased risk for introduction of bias
        ii. Missing at random indicates data that are absent and the absence is related to other patient data (e.g., correlation with age), and therefore may increase risk of bias.
        iii. Missing not at random indicates data that are absent, but the absence is not related to one of the above.
    b. There are multiple ways to handle missing data (e.g., imputation), but the method should be defined a priori given that significant amounts of missing data may introduce bias.
    c. Confounding variables must be handled in a manner that can be controlled during analysis (i.e., regression models).

C. Meta-analysis: A systematic approach to the identification and abstracting of critical information from research reports. Outcomes from a meta-analysis may include a more precise estimate of the treatment effect or risk factor for disease than the individual studies that contributed to the pooled analysis.
1. Provides examination of heterogeneity or variability in responses
2. May be applied even when the included studies are small and substantial variation exists in the issues studied, research methods, study subjects, and other factors that may affect the overall findings
3. Many meta-analyses combine results into a best estimate with statistical confidence bounds meant to summarize what is known about the clinical problem in question.
4. Pooled results may incorporate the biases of individual studies and embody new sources of bias (e.g., publication bias).

D. Adaptive trials: Increasing attention has been given to the use of adaptive trial designs. Such trials seek to increase flexibility in clinical trials by allowing for trial modification. Prespecified rules dictate modifications upon scheduled interim evaluations of the data as the trial is ongoing (BMC Med 2018;16:29).
1. Examples of adaptive designs include: Continual reassessment method; group-sequential method; sample size re-estimation; multi-arm, multi-stage population enrichment; biomarker adaptive; adaptive randomization; adaptive dose-ranging; and seamless phase I/II or II/II trials.
2. Adaptive trials seek to increase efficiency of any type of prospective trial and to minimize potential harm to patients.
3. Challenges to adaptive trials include the complexity of statistical interpretation, lack of knowledge of the scientific community about these designs, and difficulty in communication of the results.

E. Cluster randomized trials
1. Randomize groups (clusters) of subjects to either control or intervention groups
2. Require a large sample size given the intracluster correlation coefficient and resulting design effect
3. Useful in system or group-level intervention (i.e., medication diluent change for entire ICU), when individual randomization is not possible, and to prevent contamination, or the phenomenon which occurs when providers or subjects learn about the intervention during the study period and start adopting it as standard of care, whether within the treatment group or not
4. May result in recruitment bias, more baseline imbalance between groups, loss of entire clusters, or inappropriate analyses (JAMA. 2020;323(7):616-626)

F. Pharmacokinetic and Pharmacodynamic trials
  1. Studies designed to evaluate effects of unique disease states on clinically relevant pharmacokinetic and pharmacodynamic parameters
  2. Trial designs can be prospective based on predefined sampling strategies or retrospective based in routine clinical care laboratory samples (Clin Pharmacokinet 2015;7:783-95)
  3. Large study size not needed to define properties in unique patient populations
  4. Population based pharmacokinetic and pharamacodynamic studies can help define novel clinical dosing strategies in unique patient populations

G. Noninferiority trial
  1. Noninferiority trials seek to answer whether a competing treatment is no worse than the established standard therapy (JAMA 2015;313:2371-2).
    a. Example: Quetiapine is inferior to (worse than) haloperidol for hyperactive ICU delirium versus quetiapine is no worse than haloperidol by X margin.
  2. Seeks to establish utility by showing similar effectiveness while improving safety or reducing treatment burden (e.g., costs, inconvenience, labor)
  3. Analytic approach to a noninferiority trial
    a. What is an acceptable threshold for "noninferiority"?
      i. The FDA provides guidance for non-inferiority thresholds:
        (a) Establish the smallest plausible benefit of the existing standard therapy.
        (b) Insist on some preservation of the treatment effect of the standard therapy.
        (c) The FDA recommends that 50% of the standard treatment effect be preserved when evaluating mortality for thrombolytic trials.
      ii. Maximum allowable negative outcome
    b. Threats to meaningful comparisons
      i. Effect of standard treatment was not preserved. (e.g., heparin infusion does not achieve therapeutic anticoagulation)
      ii. Intention-to-treat analysis: Suboptimal administration of the standard treatment

H. Study Design Considerations
  1. Incidence versus prevalence
    a. Incidence: Measures the occurrence of a disease (or event) over a time interval
    b. Prevalence: Measures the occurrence of a disease (or event) at a fixed point in time
  2. Validity
    a. Internal
      i. Does the study design adequately test the hypothesis?
      ii. Are the study methods sound?
    b. External
      i. Is the study population representative of the clinical setting?
      ii. Are the study findings generalizable outside the study setting?
      iii. Can the study be replicated in clinical practice?
  3. Bias: Systematic error leading to an estimate of association in the study population that varies from the source population (Am J Health Syst Pharm 2008;65:2159-68)
    a. Selection bias: Systematic selection of subjects that leads to an imbalance, or an advantage, in favor of one cohort over the other

b. Observation bias: Observers (research team) are aware of the research purpose and allow this knowledge to influence interpretation of results.
c. Recall bias: Methodological error that is introduced in survey research when the participant is asked to provide recall of a past event
d. Misclassification bias: Inappropriately categorizing a group of patients with, or without, the disease/syndrome
e. Immortal time bias: Occurs when populations studied include an exposed and unexposed group without a predefined time-zero. This results in a delay before a subject is considered treated. Given that the subjects must survive up until the time of first exposure, the time before exposure is considered immortal time (Am J Respir Crit Care Med 2003;168:49-53).
f. Measurement bias: When information collected for use as a study variable is inaccurate
g. Confounding variables: Extraneous variables that influence both the dependent and the independent variable, affecting how the overall result can be interpreted
    i. Residual confounding occurs when unmeasured variables may affect overall outcome results. This can only be avoided with randomization (Int J Public Health 2010;55:701-3).
    ii. Confounding by indication occurs when a contributor to the outcome is present in those at high risk and is an indication for intervention. This results in care differences between the exposed and nonexposed groups that may be based on differences in indication for exposure (Pharmacoepidemiol Drug Saf 2003;12:551-8).
h. Bias can be minimized with sufficient planning for design, data collection, and analysis (i.e., "effect modification").

4. Sensitivity analysis: These may be used to determine robustness of study findings in different analysis methods or in the presence of unmeasured confounding. They may also be used to detect misclassification (Am J Respir Crit Care Med 2018;198:859-67).
5. Approaches to control for bias:
    a. Study design: Randomization, matching
        i. Propensity score matching
            (a) This method in theory allows for design and analysis of observational studies to mimic aspects of a randomized controlled trial.
            (b) The propensity score itself distributes observed baseline covariates similarly between treated and untreated subjects to create a certain number of matched sets.
            (c) Caution should be exercised because propensity scores ensure balance only in observed covariates, where randomization ensures balance between both observed and unobserved covariates.
    b. Analysis: Multivariable analysis, matching potential confounding variables with a controlled cohort (discussed in detail in next section)

Practice Case

Questions 2 and 3 pertain to the following case.

You are a critical care pharmacist in the medical ICU and wish to retrospectively study the safety and efficacy of four-factor prothrombin complex concentrate (4F-PCC) for coagulopathy correction in patients with end-stage liver disease. You decide on a primary outcome of in-hospital mortality and secondary outcomes of INR correction, viscoelastic test correction, and thrombotic events.

2. Which is likely the most appropriate trial design for this study?
   - A. Case-control.
   - B. Cohort.
   - C. Case series.
   - D. Pharmacokinetic trial.

3. Which would create the highest risk of bias in this study?
   - A. Selection bias – typically only patients who are bleeding receive 4F-PCC at your institution.
   - B. Measurement bias – multiple students and a pharmacy resident collected data for this study.
   - C. Misclassification bias – classification of patients as having end-stage liver disease requires manual chart review.
   - D. Observation bias – there was no blinding of those who did or did not receive 4F-PCC.

V. STATISTICAL ANALYSIS

A. Statistical analyses can be categorized into one of two main classifications: Bayesian or central tendency (frequentist)
   1. Bayesian analysis allows for incorporation of prior knowledge into current study and calculates the probability of benefit.
   2. Frequentist statistics data are presented using descriptive statistics such as the mean, variance, standard deviation, median, and interquartile range.
   3. Interpretation of studies may be different based on whether frequentist or Bayesian analyses are selected (JAMA 2019;321:654-64; Am J Respir Crit Care Med 2020;201:423-9).

B. Hypothesis Testing – Determining whether an observation or outcome was caused by chance results in either rejecting or accepting (failing to reject) a null hypothesis (H_0)
   1. Rejecting the null hypothesis results in accepting the alternative hypothesis (H_1)
   2. Null and alternative hypotheses are built according to study aim and design
      a. Superiority trial example (N Engl J Med 2023; 388:499-510).
         i. H_0 = no difference in mortality exists between a restrictive versus liberal fluid strategy for sepsis-induced hypotension
         ii. H_1 = a restrictive fluid strategy would lead to lower mortality than liberal fluid strategy for sepsis-induced hypotension
         iii. The study found no significant difference in mortality between groups, thereby resulting in a failure to reject the null hypothesis.
      b. Type I error (alpha [α] error): To reject the H_0 when, in fact, it is true. Decisional threshold to reject/not reject the H_0 is conventionally set at $\alpha = 0.05$. The α value represents the likelihood that a type I error will be made. An α set at 0.05 means that the H_1 will erroneously be accepted 1 in 20 times.

i. Two-tailed tests distribute half of the α value at the far left hand and far right hand ends of the distribution

ii. One-tailed tests distribute all of the α value at the far left hand or far right hand ends of the distribution

c. Type II error (beta [β] error): Fail to reject the H_0 when, in fact, there is a difference between groups (i.e., the H_1 is true). Decisional threshold to set β at 0.20.

d. Power (1-β): The ability to detect a difference if one truly exists. Contingent on sample size. However, this is an estimate and may be inaccurate (usually based on previous literature).

i. Sample size is the number of subjects or samples collected or assessed within a study and is influenced by the following:

(a) Treatment effect, or difference within the predicted outcomes that is considered to be clinically significant (i.e., difference in control vs. treatment group mortality rate)

(b) The variability in the predicted outcomes (i.e., the variability in baseline mortality)

(c) What is deemed to be an acceptable rate of type I error (α)

(d) Type II error rate (β)

ii. Typically the greater the effect and the lower the variability, the smaller the sample size required

iii. Decreasing the rate of type I error (α) and/or increasing the power (decreasing β) increases the necessary sample size.

Table 1. Simple Statistical Test Selection for Normally Distributed Data

Variable	Two Samples		>Two Samples	
	Independent	Related	Independent	Related
Nominal	Chi-square or Fisher exact	McNemar test	Chi-square	Cochran Q
Ordinal	Wilcoxon rank sum Mann-Whitney *U*	Wilcoxon signed rank	Kruskal-Wallis (MCP)	Friedman ANOVA
Continuous with no covariates	Student t-test Unequal variance t-test	Paired t-test	1-way ANOVA (MCP)	Repeated measures ANOVA
Continuous with one covariate	ANCOVA	2-way repeated measures ANOVA	2-way ANOVA (MCP)	2-way repeated measures ANOVA

ANCOVA = analysis of covariance; ANOVA = analysis of variance; MCP = multiple comparison procedures.

C. Types of Data and Corresponding Tests (Table 1)

1. Continuous

a. Counting, chronological order (e.g., 7.0, 7.1, 7.2, 7.3)

b. Sample tests: t-test, Wilcoxon rank sum/Mann-Whitney *U*

2. Categorical

a. Nominal

i. Categories or groups to which data are designated (e.g., race, sex, hypertension, heart failure)

ii. Sample tests: Chi-square, Fisher exact

b. Ordinal

i. Categorical data that include an order (e.g., Likert scale)

ii. Sample tests: Wilcoxon signed rank test, Wilcoxon rank sum test, Mann-Whitney *U* test, Kruskal-Wallis 1-way test

3. Descriptive statistics
    a. Measures of central tendency
    b. Mean: Used for continuous and normally distributed data (parametric), sensitive to outliers. Typically presented in conjunction with standard deviation.
    c. Median: 50th percentile, used for ordinal data or continuous and non-normally distributed data (nonparametric). Typically presented in conjunction with interquartile range.
    d. Mode: Value occurring most frequently in a distribution
    e. Standard deviation
        i. Used for continuous, parametric data
        ii. Describes variability around the mean
        iii. Approximately 95% of the data fall within two standard deviations of the mean
    f. Range: Describes spread of data, minimum to maximum values
    g. Percentiles: The value where a percentage of values falls below. Example: The 75th percentile is where 75% of values are smaller.
    h. Interquartile range: Describes the values between the 25th and 75th percentiles
        i. Used for continuous, nonparametric data
4. Paired data
    a. There are circumstances in which matching will occur naturally between data points
        i. Duplicate measurements on one sample
        ii. Sequential measurements, such as a pre-post test
        iii. Cross-over trials
        iv. Matched samples

D. Parametric Continuous Data
1. Two independent groups: Student t-test
2. Three or more groups: Analysis of variance (ANOVA)

E. Nonparametric Continuous Data
1. Two independent groups: Wilcoxon rank sum or Mann-Whitney *U*
2. Three or more groups: Kruskal-Wallis

F. Nominal Data
1. Two or more categories (e.g., sex, race, treatment groups, CAM-ICU [Confusion Assessment Method for the ICU])
2. Chi-square test
3. Fisher exact test: More accurate for smaller data sets (fewer than five observations per group)

G. Ordinal Data
1. Groups represented by scale (e.g., Richmond Agitation-Sedation Scale score, Sequential Organ Failure Assessment score)
2. Central tendency expressed as median and quartiles
3. Statistical tests: Wilcoxon rank sum, Mann-Whitney *U*, Kruskal-Wallis

H. Confidence Interval (CI)
1. A method to describe variability around a point estimate within the study population
2. CIs offer a more descriptive interpretation of the data.
    a. Magnitude of difference between groups
    b. Range of values (possible spread of point estimates)

c. A 95% CI describes the interval that would contain the true population point estimate in 95 of 100 random samples.

I. Correlation: Describes the association between two variables
   1. Correlation value (r) contains a range of values from -1 to +1. An r value of -1 or +1 indicates a perfect negative or positive relationship, respectively. Relative to 0, the closer the values are to 1, the stronger the relationship between the two variables.
   2. Pearson: Parametric continuous data
   3. Spearman rank: Nonparametric continuous data or ordinal data

J. Regression Analysis: Describes whether an independent variable can predict an outcome or the causal effect of an exposure on an outcome in the presence of possible confounders (Table 2). Can be used to describe the strength of the association between a predictor variable and a dependent variable
   1. Linear regression
      a. Used when the dependent variable is continuous (e.g., length of stay)
      b. A single predictor variable (continuous or categorical) can be tested in a simple linear regression model.
      c. More than one predictor variable (continuous or categorical) can be tested at a time in a multivariable linear regression model.
   2. Logistic regression
      a. Used when the dependent variable is a categorical variable (e.g., mortality)
      b. A single predictor variable (continuous or categorical) can be tested in a simple logistic regression model.
      c. More than one predictor variable (continuous or categorical) can be tested at a time in a multivariable logistic regression model.
   3. Considerations
      a. Selection of variables may depend on the primary goal of the regression model (predictive vs. explanatory).
         i. Variables for models that examine causal associations should be identified as possible confounders for exposure of interest that may affect the outcome.
            (a) A priori determination through literature review and anecdotes
            (b) R-squared, Mallows C(P) statistic, manual or automated (ie, backward elimination or forward selection) step-type
            (c) Directed acyclic graphs and causal networks
         ii. Selecting variables for inclusion solely on the basis of correlation between each independent variable and outcome of interest, p values on univariate analysis, or automatic variable selection (e.g., forward or backward stepwise selection) may result in overfitting or misconceptions about true confounders.
         iii. Avoid colinear variables (i.e., septic shock and vasopressor requirement may be too similar [e.g., multicollinearity])
      b. Goodness of fit may be assessed in multiple ways (R^2, Hosmer-Lemeshow tests, etc.)
         i. Must be critically assessed as goodness of fit may not completely reflect important outliers or may demonstrate overfitting
      c. Regression analyses make several key assumptions, some of which are as follows:
         i. Linear relationships between independent variables and outcome
         ii. No multicollinearity
         iii. Random component of the model is normally distributed
         iv. Appropriate number of variables for study sample size (e.g., at least around 10–20 cases per independent variable in the model)

Table 2. Statistical Regression Model According to Type of Data

Dependent Variables	Independent Variables	Test(s)
Continuous	Continuous	Linear regression
Continuous	Categorical	Linear regression
Categorical, ordinal	Continuous	Logistic regression
Categorical, ordinal	Categorical	Logistic regression

K. Measures of Effect for Categorical Data (Figure 3)
  1. Ratios with 95% CI that are used to compare the incidence of categorical outcomes are interpreted in relation to a reference point (1.0). If the 95% CI surrounding the ratio includes 1.0, the risk, odds, or hazard of the outcome is equally likely in both groups.
  2. Effect estimates are preferred to p values to assess statistical significance. P values are often misused, and effect estimates generally better describe outcomes.
  3. Relative risk (RR)
     a. Incidence of outcome in exposed group/incidence of outcome in control group
  4. Relative risk reduction (RRR)
     a. Relative difference in outcome in exposed group/relative difference in outcome in control group
  5. Absolute risk reduction (ARR)
     a. Absolute difference between outcome in exposed and control groups
  6. Odds ratio (OR)
     a. Odds of outcome occurring in group exposed to risk factor or intervention/odds of outcome occurring in control group
     b. Compares number of events or outcomes between two groups assuming that the incidence remains constant over a fixed time interval
  7. Hazard ratio (HR)
     a. Hazard rate in exposed group/hazard rate in control group
     b. Compares number of events or outcomes between two groups where the incidence varies over a time interval

$$\mathrm{RRR} = \frac{\mathrm{ARR}}{\left(\frac{C}{C+D}\right)} \qquad \mathrm{ARR} = \left(\frac{C}{C+D}\right) - \left(\frac{A}{A+B}\right) \qquad \mathrm{RR} = \frac{\left(\frac{A}{A+B}\right)}{\left(\frac{C}{C+D}\right)} \qquad \mathrm{OR} = \frac{A + D}{B + C}$$

	Outcome	**No outcome**
Exposed	A	B
Unexposed	C	D

Figure 3. Equations for measures of effect.

ARR = absolute risk reduction; OR = odds ratio; RR = risk ratio; RRR = relative risk reduction.

L. Survival Analysis (time-to-event analysis)
  1. Censoring: Adjusts data so that patients are not included (i.e., “censored”) in the analysis if they did not experience, or were not observed for, the event

2. Kaplan-Meier method
    a. Describes the impact of a single predictor variable on the time-to-event between cohorts
    b. Compares the survival times between two cohorts while controlling for a singular predictor variable
    c. Survival curves are typically analyzed using the log-rank test.
    d. Results typically reported as hazard ratio with 95% CI
3. Cox proportional hazards model
    a. Describes the impact of several predictor variables on the time-to-event
    b. Compares the survival times between two cohorts while controlling for several predictor variables
    c. Results typically reported as hazard ratio with 95% CI

M. Determining Predictive Ability (Figure 4)
1. Sensitivity: Probability of identifying a true positive from a group that is known to be positive
    a. Avoiding false negatives
    b. Example: Proportion of people with disease correctly identified as having the disease through laboratory assay
2. Specificity: Probability of identifying a true negative from a group that is known to be negative
    a. Avoiding false positives
3. Positive predictive value (PPV): Probability of identifying a true positive from a group that may or may not be positive
    a. Avoiding false positives
    b. Example: Proportion of people with positive laboratory assay result who actually have the disease
4. Negative predictive value (NPV): Probability of identifying a true negative from a group that may or may not be negative
    a. Avoiding false negatives

$$\text{Sensitivity} = \frac{A}{A + C} \times 100 \qquad \text{PPV} = \frac{A}{A + B} \times 100$$

$$\text{Specificity} = \frac{D}{B + D} \times 100 \qquad \text{NPV} = \frac{D}{C + D} \times 100$$

	Has disease or outcome	**Does not have disease or outcome**
Positive	A	B
Negative	C	D

Figure 4. Equations for determining predictive ability.

NPV = negative predictive value; PPV = positive predictive value.

Practice Case

Questions 4–6 pertain to the following case.

The neurosurgery physician group at your institution would like your input in evaluating the usefulness of procalcitonin for distinguishing neurogenic fevers from true infectious etiologies of fever. An additional goal of the study would be to evaluate risk factors and possible confounders for positive and negative procalcitonin values. You decide on a predictive cutoff of 0.5 ng/mL (positive 0.5 mg/mL or greater; negative less than 0.5 ng/mL).

4. Which statistical test would be most appropriate to evaluate any difference in creatinine clearance (milliliters per minute) between patients with positive and negative procalcitonin?
   A. Chi-square.
   B. Wilcoxon signed rank.
   C. Student t-test for parametric data.
   D. Mann Whitney *U* for parametric data.

5. Which statistical test would be most appropriate to determine an independent association between positive procalcitonin and true infection in the presence of possible confounders?
   A. Linear regression.
   B. Logistic regression.
   C. Cox proportional hazards model.
   D. Correlation analysis.

6. You enroll 201 patients who have a true infection and 200 patients who are not infected. Of the 201 with infection, 189 have a positive procalcitonin and 12 have a negative procalcitonin. Of the 200 patients without infection, 100 have a positive procalcitonin and 100 have a negative procalcitonin. Which best describes the sensitivity and specificity of procalcitonin in this population?
   A. 94% sensitivity and 89% specificity.
   B. 65% sensitivity and 89% specificity.
   C. 65% sensitivity and 50% specificity.
   D. 94% sensitivity and 50% specificity.

VI. APPLICATION OF KNOWLEDGE TO PATIENT CARE

A. Integration of Various Types of Knowledge (Table 3)

Table 3. Assessment of Primary Literature for Clinical Application

	Assessment
Study design	• Were the hypotheses and study purpose clearly stated? • Is the study sample representative of the population with the disease/syndrome? • Are the inclusion/exclusion criteria too restrictive? • Did the study meet power? Was a sample size calculation described? • How were blinding and randomization conducted? • Is the study design translatable to clinical practice? • How were the primary and secondary end points defined? Have those definitions been validated in critically ill patients?
Outcomes	• Is the primary outcome scientifically valid and patient-centered? • Are the secondary outcomes clearly described? • How were adverse effects defined and analyzed?
Analysis	• Were the statistical tests appropriate? • How were the data analyzed (intention-to-treat, per-protocol, as-treated)? • How large was the treatment effect? • Will the effect size be duplicated in clinical practice? • Did the author(s) provide an interpretation of the study findings and describe them in the context of the available knowledge?

1. Medical literature
   a. Remaining current with evolving literature is a necessary skill for the critical care clinician.
   b. Knowledge gained from primary literature can be objective, can limit bias, and may be translatable compared with experiential knowledge.
   c. The findings of clinical research can be limited to the conditions of the study and may not easily confer the same benefit in clinical practice.
      i. Number needed to treat (NNT) – Quantifies the anticipated effect of a treatment in a patient population on the basis of study results. A low number signifies an effective treatment; a high number indicates a less effective therapy. NNT = 1/ARR
      ii. Number needed to harm (NNH) – Quantifies the associated harm after exposure to a treatment. A low number signifies a harmful treatment; a high number indicates a safer treatment. NNH = 1/attributable risk
   d. The study results limit the findings attributable to chance but may not fully exclude chance. Remember: Studies are conducted in samples and may or may not be representative of the population.
   e. Fragility index: The number of non-events in the overall sample that need to occur to render a significant result nonsignificant. In the CRICS-TRIGGERSEP trial, an additional three events for the outcome of 90-day mortality would have rendered the trial findings nonsignificant (shifting to a p=0.053), indicating the fragility of the final results (N Engl J Med 2018;378:809-18).
2. Experiential knowledge
   a. Knowledge accumulated through clinical experience and for a sustained period is valuable.
   b. How does an individual patient differ from the patient sample of the study being applied?
   c. When possible, this type of knowledge should be reinforced with scientific evidence. Example: N Engl J Med 2009;361:1925-34
3. Pathophysiologic reasoning
   a. Application of physiologic concepts to drive or reinforce therapeutic choices

  b. Can aid in determining short-term goals. Example: Selecting an initial dose of loop diuretic according to the home medication dose and current therapeutic goal of urinary output
  c. Primary literature on which to base treatment decisions for all clinical scenarios may not exist.

B. Synthesizing the Available Evidence to Develop Treatment Protocols
  1. Protocols are intended to synthesize the best available evidence and standardize a series of treatment options to reduce variability and error while maximizing treatment effect. Examples: Sterile technique for central line placement, heparin or insulin infusions, and sepsis bundles.
  2. Determining which literature to incorporate and its applicability to the local practice environment is key.
  3. Determine the homogeneity of various studies on the same topic (e.g., early goal-directed therapy for septic shock) and confounding variables that influence the interpretation of results. Study design affecting the screening and time to treatment for subjects compared with actual practice, improvements in the processes of usual care over time, etc.

C. Unique Factors That Promote/Impede the Application of Treatment Protocols
  1. Resource use
    a. Personnel (e.g., Lancet 2010;375:475-80)
    b. Drug shortages
    c. Fiscal
  2. Ease of protocols
    a. Complexity
    b. Familiarity
  3. Lack of consensus (e.g., sepsis 1-hour bundle)

Practice Case

Questions 7 and 8 pertain to the following case.
You are reading a study that evaluated the use of hydrocortisone versus placebo for lowering C-reactive protein (CRP) in patients with ARDS at 3 days after enrollment. The authors concluded that they would need to enroll 100 patients to achieve 90% power to find a decrease in CRP of 10 mg/L, assuming a baseline concentration of 35 mg/L and an α level of 0.05. They enroll 50 patients in the hydrocortisone group and 51 patients in the placebo group. The median [interquartile range] CRP concentrations in the intervention and placebo groups are 23 [19–31] and 29 [20–40], respectively ($p<0.05$). The percentages of patients achieving a CRP decrease of at least 10 mg/L in the intervention and placebo groups are 15% and 18%, respectively ($p>0.05$).

7. Which is your biggest concern with interpreting the validity of this study?
   A. The study did not meet statistical power.
   B. The sample size is too small to provide a representative population for the disease state.
   C. The outcome of lowering CRP should not be dichotomized, but only analyzed as a continuous variable.
   D. The outcome of CRP is a surrogate and likely not a good representation of the clinical implications of steroid use in ARDS.

8. Which best describes the NNT for achieving a CRP decrease of at least 10 mg/L in this study?
   A. 34.
   B. 17.
   C. 50.
   D. 6.

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ANSWERS AND EXPLANATIONS TO PRACTICE CASE QUESTIONS

1. **Answer: D**

This study requires consideration of options A, B, and C. Informed consent may be waived because both drugs may be considered standard of care, but some IRBs at various institutions may require the use of community consent measures; obtaining informed consent directly from the patient or a family member may be impossible due to the acute nature of the intervention. Differences in local perceptions on why patients may be agitated on presentation to the emergency department could lead to heterogeneity in use of the study agents, affecting results downstream. In addition, a multicenter trial creates a risk of differences in patient characteristics during enrollment that may need to be controlled for in the study. Option D is not a valid practical consideration based on the study design. The cluster crossover trial may compare two known standards of care, and the crossover design allows for hospitals/units to serve as their own controls. Risk of bias is never zero, but blinding would not introduce unnecessary bias into this trial's results (Answer D is correct; Answers A, B, and C are incorrect).

2. **Answer: B**

The study goal is to determine whether exposure to 4F-PCC resulted in mortality, or the outcome of interest. This is performed in a cohort of patients who all have end-stage liver disease (Answer B is correct). A case-control study involves structuring study groups by those who did and did not have an outcome of interest in order to determine relevant risk factors leading to that outcome (Answer A is incorrect). A case study would be better suited to a single group without a comparator and is typically used to describe a novel intervention or outcome (Answer C is incorrect). Pharmacokinetic trials typically involve sample collection and evaluation of drug concentrations to describe the kinetics of the drug as opposed to clinical outcomes (Answer D is incorrect).

3. **Answer: A**

If patients who are bleeding more often receive 4F-PCC according to institutional standards or physician preference, there is likely a difference in the severity of illness between the two study groups (those who did and did not receive 4F-PCC), which could lead to selection bias in the result of mortality (Answer A is correct). Although measurement bias is possible because of multiple people collecting data, it is less likely to have as large an impact on the outcomes as long as a data collection plan is implemented and followed (Answer B is incorrect). Misclassification bias is also possible but is less likely to affect outcomes at the same magnitude as selection bias as long as a consistent data collection and chart review plan is followed (Answer C is incorrect). Observation bias would likely be more important in a prospective trial than in a retrospective trial to blind those involved to ensure all other standards of care are followed (Answer D is incorrect).

4. **Answer: C**

Student t-test is appropriate to compare two independent means as a measure of parametric or normally distributed data (Answer C is correct). A chi-square analysis is used for categorical data (Answer A is incorrect). Wilcoxon signed rank is used to compare two related medians as a measure of nonparametric data (Answer B is incorrect). Mann-Whitney *U* is used to compare two independent medians as a measure of nonparametric data (Answer D is incorrect).

5. **Answer: B**

A regression analysis can be used to identify independent associations in the presence of other risk factors for the outcome. Logistic regression is used when the outcome of interest (i.e., patients with positive or negative procalcitonin) is categorical in nature (Answer B is correct). Linear regressions are used similarly to logistic regressions for a continuous dependent variable (Answer A is incorrect). A Cox proportional hazards model is used as a survival analysis or time-to-event analysis, which would not be applicable to the outcome or question in this case (Answer C is incorrect). Although a correlation could determine the strength of association between positive procalcitonin and infection, it would not consider other risk factors that could be confounding the results (Answer D is incorrect).

6. **Answer: D**

The sensitivity is around 94%, and the specificity is 50% (Answer D is correct). The sensitivity is calculated by dividing 189/201, and the specificity is calculated by dividing 100/200. The PPV is around 65%, and the NPV is around 89% (Answers A, B, and C are incorrect). The PPV is calculated by dividing 189/289, and the NPV is calculated by dividing 100/112.

7. **Answer: D**

When evaluating this study, it is important to consider that the outcome related to a biomarker is simply a surrogate as opposed to a true clinical outcome. This could be problematic or lack validity because other steroids have previously been studied for outcomes such as mechanical ventilator days and mortality (Answer D is correct). The study may not have met the criteria for the original power analysis that was defined by the authors, but it did achieve power to find a statistically significant difference according to the outcome (Answer A is incorrect). Although the sample size is small, it may represent a reasonable population with internal validity to use the information in a limited way, particularly at the institution(s) where it was performed (Answer B is incorrect). The power analysis was created around a continuous outcome, but it is reasonable to present the data in two different ways (in this case, patients who did and did not achieve a CRP decrease of at least 10 mg/L) as long as the reader understands that the study was not powered around this analysis (Answer C is incorrect).

8. **Answer: A**

The NNT is calculated by 1/ARR. The absolute risk reduction is 3%, or 0.03. The NNT is 1/0.03 = 34 (rounding up to the nearest whole number) (Answer A is correct; Answers B, C, and D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

This study seeks to compare two viable treatments of hypovolemic shock in trauma patients. Because subject identification would be trauma patients from the community and treatment would be initiated in the field, potential harm is associated with each treatment, and it is expected that many potential patients would lack decisional capacity at the time of informed consent. Although treatment blinding is an essential component to trial design to limit investigator and clinician bias, it is not an ethical consideration (Answer A is incorrect). Given the incidence of trauma in the general population and its burden on society, treatments to improve the outcomes of trauma patients are necessary and informative (Answer B is incorrect). Acknowledging the limited supply of blood products, a superiority trial is essential to help steward the use of a finite resource (Answer D is incorrect). The issue of informed consent in this study is challenging, but the issue needs to be addressed for the ethical conduct of this study (Answer C is correct). There is precedent for this trial to receive an exception for informed consent requirements under the FDA code of regulations.

2. **Answer: C**

The study seeks to establish the effectiveness of a novel drug compound for septic shock. This is challenging because of the dramatic improvements in 28-day mortality during the past decade. To show the effectiveness of a novel drug compound, the drug should be tested in a representative population of patients with the disease. Excluding patients because of baseline comorbidity would limit external validity (Answer A is incorrect). Including patients with sepsis, which has a lower 28-day mortality rate than septic shock, would not address the issue of an appropriate end point (Answer B is incorrect). Limiting study inclusion to patients with a pneumonia etiology would be inappropriate unless the pharmacology of the novel drug specifically targeted pneumonia pathophysiology (Answer D is incorrect). Answer C is correct as the anticipated incidence of mortality has changed overtime as well as the likely anticipated minimum detectable effect. With all other assumptions remaining equal, the authors will have to increase enrollment to find the effect relative to previous trials.

3. **Answer: B**

A QI study would likely show the effectiveness using a pre/postintervention cohort design. In this type of study, informed consent is generally not required because the treatment is provided to all patients as a standard of care (Answer A is incorrect). A community advertising campaign might improve the delivery of care and improve patient adherence, but it is unnecessary to measure the effectiveness of the QI initiative (Answer C is incorrect). The QI initiative is believed necessary and has therefore been deemed to have intrinsic social value (Answer D is incorrect). To show the effectiveness of the intervention, the syndrome must be recognized before initiating treatment (Answer B is correct).

4. **Answer: C**

To effectively determine the incidence and clinical impact of adverse drug events on clinical outcomes in the ICU, it would be unethical to randomize patients to experience the event (Answer A is incorrect). A retrospective design would not be ideal because of the limitations in data extraction, assignment of events, and interpretation of causality (Answers B and D are incorrect). A prospective observational design would allow the investigator team to identify the incidence of adverse events, sequential outcomes, and determine causality (Answer C is correct).

5. **Answer: D**

A correct interpretation of the results is recognizing that even though the OR suggests an associated increase of 30% in the risk of being exposed to CDI, the 95% CI crosses 1, meaning that the odds of exposure to CDI are as likely to increase the risk as to decrease that risk (Answer D is correct; Answers A–C are incorrect).

6. **Answer: B**

Use of albumin reduced the odds of mortality (and conversely, increased the odds of survival) with an OR of 0.45, and the 95% CIs were all less than 1 in treating hypovolemic shock in trauma. In addition, the OR was 1.1 for septic shock, whereas the 95% CI crossed 1, showing that the odds were as likely that albumin increased mortality as that it reduced it (Answer B is correct). Because the OR and the 95% CI for treating hypovolemic shock are both less than 1, mortality was decreased with albumin use (Answers A, C, and D are incorrect).

7. **Answer: A**

This patient case provides a practical example of a critical care pharmacist's integration of various types of knowledge to optimize patient care. The FACT trial showed that a fluid-conservative strategy improves ventilator-free days for patients with acute lung injury and ARDS. Furosemide was used in the study to show the outcome benefit. However, the study was testing a treatment strategy, not specifically a drug strategy. Therefore, it can be reasoned that similar treatment outcomes can be shown with similar drugs if the study drug is unavailable – in this case, because of drug shortage. Knowledge of trial design is helpful but not critical to optimizing this patient's therapy with bumetanide (Answer B is incorrect). Hemodialysis is invasive, requires finite resource use, and has an associated morbidity risk (Answer C is incorrect). Because this patient case does not include a broader hypothesis test in a systematic design, this is not a research activity, and informed consent is not required (Answer D is incorrect). A critical care pharmacist, using knowledge of the FACT trial (medical knowledge) together with an understanding and experience with bumetanide therapy (experiential knowledge), can develop a treatment plan (Answer A is correct).

8. **Answer: A**

Acute respiratory distress syndrome is a clinical syndrome with an associated mortality with each progressing phase (mild, moderate, and severe). Although ARDS is also a constellation of findings and pathologic observations, patients with this disease present with a similar finding of severe, refractory hypoxia from a common etiology (Answer B is incorrect). Given the associated mortality of about 45% for severe ARDS, a finite resource should be prioritized for it (in this case, a NMBA) (Answer C is incorrect). Mortality/survival is readily identified as an end point of social value for research design (Answer D is incorrect). Given the relatively low mortality associated with mild ARDS (around 20%) compared with severe ARDS (around 45%), and mortality benefit was seen only in the subgroup of patients with severe ARDS, administering NMBAs would less likely improve survival and more likely increase harm if systematically administered to patients with mild ARDS (Answer A is correct).

FLUIDS, ELECTROLYTES, ACID-BASE DISORDERS, AND NUTRITION SUPPORT

ASHLEY HAWTHORNE, PHARM.D., BCCCP

AUBURN UNIVERSITY HARRISON COLLEGE OF PHARMACY
AUBURN, ALABAMA

Fluids, Electrolytes, Acid-Base Disorders, and Nutrition Support

Ashley Hawthorne, Pharm.D., BCCCP

Auburn University Harrison College of Pharmacy

Auburn, Alabama

Learning Objectives

1. Describe normal fluid requirements and common patient conditions that alter fluid needs and homeostasis.
2. Develop an appropriate assessment and treatment plan for common electrolyte disorders in critically ill patients.
3. Correctly identify complex acid-base disorders based on a patient's laboratory data and clinical course.
4. Specify the appropriate route (parenteral or enteral) of nutrition administration, energy and protein needs, and key micronutrients to be provided to a critically ill patient.
5. Develop an appropriate assessment of the tolerance, safety, and efficacy of an enteral or parenteral nutrition regimen.

Abbreviations in This Chapter

ABG	Arterial blood gas
ADH	Anti-diuretic hormone
AG	Anion gap
AKI	Acute kidney injury
APACHE	Acute physiology and chronic health evaluation (score)
BEE	Basal energy expenditure
BG	Blood glucose
BMI	Body mass index
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CRRT	Continuous renal replacement therapy
COVID-19	Coronavirus disease 2019
CSWS	Cerebral salt wasting syndrome
CVP	Central venous pressure
ECF	Extracellular fluid
EDVI	End-diastolic volume index
EN	Enteral nutrition
GRV	Gastric residual volume
HCO_3	Bicarbonate
IBW	Ideal body weight
ICF	Intracellular fluid
ICU	Intensive care unit
ILE	Injectable lipid emulsion
K	Potassium
NA	Sodium
NB	Nitrogen balance
NG	Nasogastric
NPO	Nil per os (nothing by mouth)
NRS	Nutrition risk screening (score)
NUTRIC	Nutrition Risk in the Critically Ill (score)
Pco_2	Partial pressure of carbon dioxide
PCWP	Pulmonary capillary wedge pressure
PN	Parenteral nutrition
Po_2	Partial pressure of oxygen
REE	Resting energy expenditure
SCR	Serum creatinine
SIADH	Syndrome of inappropriate antidiuretic hormone
SOFA	Sequential organ failure assessment (score)
TBI	Traumatic brain injury
UUN	Urine urea nitrogen
WT	Body weight

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. Which is the most appropriate indication for parenteral nutrition (PN)?
   A. Severe anorexia.
   B. Lack of bowel sounds.
   C. Ileus.
   D. Gastric residual volume (GRV) of 300 mL.

2. Which fluid option would most closely match the composition of nasogastric (NG) fluid losses?
   A. 0.9% sodium chloride and potassium chloride 20 mEq/L.
   B. 0.45% sodium chloride and potassium chloride 20 mEq/L.
   C. 5% dextrose in 0.225% sodium chloride and potassium chloride 20 mEq/L.
   D. Lactated Ringer solution.

3. A patient with prolonged, intractable diarrhea would most likely have excess losses of which trace mineral?
   A. Zinc.
   B. Copper.
   C. Iodine.
   D. Manganese.

4. A 70-year-old man admitted to the intensive care unit (ICU) for sepsis was recently given a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) secretion. His serum sodium fell from 130 mEq/L to 115 mEq/L during the past 3 days, and his course was subsequently complicated by a seizure. Which would be the most appropriate treatment option?
   A. Intravenous 0.9% sodium chloride.
   B. Intravenous desmopressin acetate (DDAVP).
   C. Intravenous 3% sodium chloride.
   D. Intravenous conivaptan.

5. Other than the absorption/infusion rate, which best explains why enteral potassium administration is safer than parenteral potassium administration?
   A. Bioavailability of potassium is significantly lower with enteral versus parenteral administration.
   B. Feed-forward sensing of changes in mesenteric potassium concentration increases urinary potassium excretion.
   C. Potassium chloride elixir is likely to cause diarrhea and reduce potassium absorption.
   D. Wax matrix tablets sequester potassium release throughout the gastrointestinal (GI) tract.

6. A 40-year-old man (weight 60 kg) is admitted to the trauma ICU after a motor vehicle collision. He is noted to have a serum magnesium concentration of 1.2 mg/dL, and his family states that he has a history of alcohol use disorder (12–18 beers/day). He is given magnesium sulfate 6 g intravenously for 6 hours by the primary service. His repeat serum magnesium concentration on the following day is 1.8 mg/dL. Which would be the most appropriate treatment for this patient?
   A. No treatment is necessary because his serum magnesium concentration is normal.
   B. If a repeat serum magnesium concentration is 2 mg/dL or greater, no additional magnesium therapy is indicated.
   C. Supplemental calcium therapy should be given concurrently with the magnesium therapy.
   D. Additional magnesium therapy should be given daily for the next 4–5 days.

7. A 45-year-old man (weight 78 kg) with a history significant for hypertension and pancreatitis is admitted to the ICU after operative management of necrotizing pancreatitis. He is given PN consisting of 650 g of dextrose, 120 g of amino acids, and 55 g of injectable lipid emulsion (ILE) daily. Blood glucose (BG) measurements over the past 24 hours have been 180-325 mg/dL. Which change to this patient's nutrition regimen is most appropriate at this time?
   A. Initiate a sliding-scale insulin regimen with insulin aspart every 4 hours.
   B. Temporarily decrease the dextrose dose in the PN to 200 g and advance to dextrose 650 g once blood glucose is less than 180 mg/dL.
   C. Decrease dextrose to 500 g and make up with remaining kilocalories by increasing protein to 160 g.
   D. Decrease dextrose to 315 g and reassess glycemic control over the next 24 hours.

8. A 48-year-old man is admitted to the trauma ICU after a motorcycle collision. His injuries include a subarachnoid hemorrhage, right pneumothorax, multiple rib fractures, grade 5 liver laceration, right sacral fracture, and transverse process fractures. His course is complicated by respiratory failure, acute kidney injury (AKI), and hyperglycemia. His labs today reveal serum sodium 141 mEq/L, chloride 102 mEq/L, carbon dioxide 20 mEq/L, and lactate 2.6 mmol/L. His arterial blood gas values are as follows: pH 7.46, P_{CO_2} 31 mmHg, and HCO_3 22 mEq/L, Which of the following assessments of his acid-base status is correct?
   A. Primary respiratory alkalosis only.
   B. Primary respiratory alkalosis with underlying metabolic acidosis.
   C. Primary metabolic alkalosis with underlying respiratory alkalosis.
   D. Primary metabolic acidosis only.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 2
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 6, 8
    b. Task B: 5, 9, 13-15
    c. Task C: 1, 3, 4
3. Domain 3: Professional Practice
    a. Task A: 3
    b. Task B: 1, 7

I. FLUIDS AND ELECTROLYTES

A. General Overview
  1. Body water compartments
    a. Total body water (TBW): About 60% of body weight for men; about 50% of body weight for women; lower percentage for those with obesity and for older adults (0.5 L/kg for men; 0.45 L/kg for women)
    b. About 60% of TBW is intracellular.
    c. About 40% of TBW is extracellular water (about 75% is interstitial fluid; about 25% plasma volume).
    d. Fluid compartments are separated by membranes that are freely permeable to water. The movement of fluids through these compartments is due to hydrostatic pressure or osmotic pressure.
  2. Estimating daily fluid requirements
    a. Simple, weight-based estimation: 30–35 mL/kg (overestimates needs for patients with higher BMI; underestimates needs for patients with lower BMI)
    b. Holliday-Segar formula: 100 mL/kg for the first 10 kg, 50 mL/kg for the next 10 kg, and 20 mL/kg thereafter
    c. Increased insensible losses occur with diarrhea and fever (around 10%–15% for every degree Celsius greater than 37°C).
    d. Fluids received from other sources should be considered when estimating a patient's fluid needs to avoid fluid overload.

Table 1. Effect of Body Temperature on Insensible Fluid Losses (Surgery 1968;64:154-64)

Rectal Temperature (°C)	No. of Patients	Mean Fluid Loss (mL/m^2/day)
36.7–37.7	205	552
37.8–38.2	160	600
38.3–38.8	48	768
38.9–40	14	840

  3. Estimating electrolyte requirements
    a. Approximate electrolyte concentrations in the extracellular and intracellular fluids (ECFs and ICFs) (Fluid, Electrolyte, and Acid-Base Disorders, Vol 1. New York: Churchill Livingstone, 1985:1-38)

Table 2. Electrolyte Concentrations in the ECF and ICF

Electrolyte	Extracellular Fluid (mEq/L)	Intracellular Fluid (mEq/L)
	(plasma)	(muscle)
Sodium	140	12
Potassium	4.5	160
Chloride	104	2
Bicarbonate	24	10
Calcium	5.0 (10 mg/dL)	—
Magnesium	1.5 (1.8 mg/dL)	34
Phosphate	2 (3.5 mg/dL)	54

b. “Normal” daily requirements

Table 3. “Normal” Daily Requirements (Medicine (Baltimore) 1981;60:339-54; Crit Care Med 1995;23:1504-11; Ann Rev Med 1981;32:245-59; Ann Surg 1983:197:1-6)

Electrolyte	Daily Requirements
Sodium	50–150 mEq (1–2 mEq/kg)
Potassium	0.5–1.5 mEq/kg
Phosphorus	10–30 mmol
Magnesium	8–32 mEq
Calcium	10–15 mEq
Chloride[a]	80–120 mEq
Acetate[a]	80–120 mEq

[a] Depending on the acid-base status of the patient.

c. Approximate electrolyte content of GI secretions (in milliequivalents per liter) (About Surgery: A Clinical Approach. Philadelphia: Elsevier Health Sciences, 1996:5-17; Acta Chir Scand Suppl 1963:suppl 306:301-65)

Table 4. Electrolyte Content of GI Secretions

Fluid	Average Daily Volume (mL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Magnesium (mEq/L)
Stomach	1000–2000	60–90	10–15	100–130	—	0.9
Duodenum	400–600	140	5–10	90–120	80	—
Jejunum/Ileum	2000–2500	140	5–10	90–120	30–40	6–12
Colon	< 300	60	20–30	50	—	6–12
Pancreas	600–800	140	5–10	75	115	0.4
Bile	300–600	140	5–10	100	30	1.1

d. Electrolyte composition of common intravenous solutions (in milliequivalents per liter)

Table 5. Electrolyte Composition of Common Intravenous Solutions

Solutions	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Osmolarity (mOsm/L)
5% dextrose in water	—	—	—	—	—	—	252
0.45% sodium chloride (one-half normal saline)	77	—	77	—	—	—	154
5% dextrose in 0.45% sodium chloride (5% dextrose in one-half normal saline)	77	—	77	—	—	—	406
Lactated Ringer solution	130	4	109	28	2.7	—	274
Plasma-Lyte A/Normosol-R pH 7.4	140	5	98	27	—	3	294–295

Table 5. Electrolyte Composition of Common Intravenous Solutions (*Continued*)

Solutions	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Bicarbonate (mEq/L)	Calcium (mEq/L)	Magnesium (mEq/L)	Osmolarity (mOsm/L)
0.9% sodium chloride (normal saline)	154	—	154	—	—	—	308
3% sodium chloride (hypertonic saline)	513	—	513	—	—	—	1026

B. Water and Sodium Disorders
  1. Dehydration: Signs and symptoms include decreased urine output (unless patient has glycosuria or diuretic therapy), increased blood urea nitrogen/serum creatinine ratio (BUN/SCr greater than 20), insufficient net fluid balance (from intake and output documentation records), increased serum sodium, poor skin turgor, dry mucous membranes, orthostatic hypotension, “contraction alkalosis,” increased losses
     a. Fever
     b. Skin losses through sweating
     c. GI fluid losses (e.g., emesis, gastric suction, diarrhea, enterocutaneous fistula, surgical wounds, drains)
  2. Volume excess: Signs and symptoms include peripheral/sacral/pulmonary edema, anasarca, rapid weight gain, positive fluid balance
     a. Excessive fluid and/or sodium intake
     b. Impaired ability to excrete excess water and sodium (e.g., heart failure, cirrhosis with ascites, renal failure)
  3. Hyponatremia (see also the Neurocritical Care chapter for further reading on hyponatremia)
     a. Classic evaluation
        i. Exclude hyperglycemia, mannitol, and glycine for unmeasured effective osmoles (hypertonic hyponatremia).
           (a) Correct serum sodium for hyperglycemia (once the hyperglycemia is controlled, the serum sodium will rise).
              (1) For every 100-mg/dL increase in BG greater than 100 mg/dL, serum sodium will fall by about 2.4 mEq/L (or vice-versa).
              (2) Corrected serum Na = Measured serum Na + [(BG -100)/100 * 2.4] (Am J Med 1999;106:399-403).
        ii. Exclude factitious/pseudo-hyponatremia (isotonic hyponatremia): Arguably still possible during lipemia (triglycerides greater than 1000 mg/dL or hyperproteinemia (e.g., multiple myeloma) if the serum is diluted under the assumption that the serum contains 7% solid-phase particles before the assay (Intensive Care Med 2014;40:320-31).
        iii. Evaluate ECF volume (increased, normal, decreased): Evaluate patient for edema, fluid balance on fluid intake/output records, hemodynamic markers, chest radiography: Pulmonary infiltrates without pneumonia, enlarged heart or evidence of diseases with decreased urinary water/sodium excretion (e.g., AKI, congestive heart failure, cirrhosis with ascites).
        iv. European guidelines suggest evaluating urine sodium and osmolality before ECF volume because ECF volume is difficult to determine in the critically ill patient (*Intensive Care Med.* 2014;40(3):320-331).
        v. Evaluate urine sodium and osmolality for hypotonic (serum osmolality less than 280 mOsm/kg) hyponatremia in conjunction with volume status (hypovolemic, euvolemic, hypervolemic):

Table 6. Comparative Features of Hypotonic Hyponatremia (Am J Med 2013;126:S1-42)

ECF volume status	Hypervolemic		Euvolemic		Hypovolemic	
Physiologic Findings	Edema, large positive fluid balance, pulmonary infiltrates without pneumonia, enlarged heart, increased PCWP, EDVI		No evidence of fluid overload or dehydration, fluid equilibrium, normal hemodynamics		Poor skin turgor, dry mucous membranes, decreased urine output, concentrated urine, tachycardia, increased BUN/SCr ratio	
Urine Osm (mOsm/kg)	> 100		< 100	> 100	> 450	
Urine Na (mEq/L)	< 20	>20	< 20	> 20	< 20	>20
Potential etiologies	CHF, Cirrhosis with ascites, Nephrotic syndrome	Renal failure	Psychogenic polydipsia, Excessive hypotonic fluid intake, Beer potomania	SIADH,[a] Cortisol deficiency, Hypothyroidism, Drug-induced	Extra-renal losses (e.g., GI fluid losses), Third space losses	Diuretics, Adrenal insufficiency, Cerebral salt wasting, Thiazide diuretics, Salt wasting nephropathy

[a] Common etiologies for SIADH (Am J Kidney Dis 2008;52:144-53; Hosp Pharm 2002;37:1336-42):
Central nervous system (CNS) disorders – Trauma, stroke, infection, brain tumors
Malignancy – Small cell carcinoma of the lung, pancreatic carcinoma, lymphoma, Hodgkin disease, sarcoma
Pulmonary infection, respiratory failure with positive pressure ventilation
Endocrine disorders – Pituitary tumor, hypothyroidism, adrenal insufficiency
Stress response (surgery, trauma, thermal injury, sepsis, pain)
Drugs

BUN=blood urea nitrogen; CHF = congestive heart failure; EDVI = end-diastolic volume index; GI = gastrointestinal; PCWP = pulmonary capillary wedge pressure; SIADH = syndrome of inappropriate antidiuretic hormone.

Table 7. Drug-Induced SIADH (*JAMA*. 2022;328(3):280-291)

Mechanism	Examples
Increased hypothalamic production of ADH	Amitriptyline, imipramine
	Thioridazine, trifluoperazine
	Haloperidol
	Carbamazepine, oxcarbazepine, valproic acid
	Vincristine, vinblastine, cisplatin, carboplatin, ifosfamide, methotrexate
	Nicotine
	Bromocriptine
	Monamine oxidase inhibitors
Increased sensitivity to or exogenous administration of ADH	DDAVP, desmopressin
	Lamotrigine

Table 7. Drug-Induced SIADH (*JAMA*. 2022;328(3):280-291) (*Continued*)

Mechanism	Examples
Mixed or uncertain	Opiates
	Barbiturates
	Nonsteroidal anti-inflammatory agents
	Angiotensin-converting enzyme inhibitors
	SSRIs
	Cyclophosphamide
	MDMA

ADH = antidiuretic hormone; MDMA = methylenedioxymethamphetamine; SSRI = selective serotonin reuptake inhibitor.

vi. If the patient has a TBI, it can be difficult to ascertain whether the patient has cerebral salt wasting syndrome (CSWS) or SIADH. The main difference between these 2 clinical scenarios is the patient's volume status. Those with CSWS are typically hypovolemic, whereas those with SIADH are euvolemic.

Table 8. Comparison of Features of Hyponatremia Caused by CSWS vs. SIADH (Hosp Pharm 2002;37:1336-42)

CSWS	SIADH
Decreased serum sodium	
Decreased ECF	Normal or expanded ECF
Negative sodium balance	Variable sodium balance
CVP/PCWP/EDVI decreased	CVP/PCWP/EDVI normal or increased
Urine osmolality increased	
Urine sodium increased	

CVP = central venous pressure; CSWS = cerebral salt wasting syndrome; ECF = extracellular fluid; EDVI = end diastolic volume index; PCWP = pulmonary capillary wedge pressure.

b. Treatment of hyponatremia

i. Typically reserved for acute (less than 48 hours) hyponatremia and/or severe symptoms (mental status changes, coma, or seizures, regardless of chronicity) (Am J Med 2013;126:S1-42). Immediate treatment with hypertonic saline therapy (3% NaCl) should be adjusted to achieve a serum Na concentration increase of 5 mEq/L in the first hour, and limit to a total of 10 mEq/L increase during the first 24 hours and additional 8 mEq/L during every 24 hour thereafter until serum sodium reaches 130 mEq/L (Intensive Care Med 2014;40:320-31). More rapid correction could lead to central pontine myelinolysis. An updated guideline recommendation from the American Society of Nephrology recommends considering the risk of central pontine myelinolysis to further determine correction goals. Patients with heightened risk include those with a sodium of 105 mEq/L or less, alcohol use disorder, hypokalemia, malnutrition, and advanced liver disease. Discontinue hypertonic saline when goal serum sodium change has been achieved or symptoms have improved (whichever occurs first).

(a) Hypertonic saline dose and administration – Intermittent bolus versus continuous infusion:

(1) Intermittent boluses: 3% NaCl 150 mL (or 2 mL/kg) intravenously over 20 minutes ×3 (Intensive Care Med 2014;40:320-31) or 100 mL intravenously over 10 minutes ×3 (Am J Med 2013;126:S1-42)

(2) Continuous infusion: 3% NaCl 20 mL/hour (JAMA Intern Med 2021;181:1-12; J Clin Endocrinol Metab 2019;104:3595-602) or 0.5–2 mL/kg/hour (Am J Med 2013;126:S1-42)

Table 9. Sodium Correction Goals According to Risk of Central Pontine Demyelination

Scenario	24-h correction (mEq/L)	48-h correction (mEq/L)
Normal risk (chronic hyponatremia with Na ≤ 120 mEq/L)	Max: 10-12 Min: 4-8	Max: 18
Heightened[a] risk	Max: 8 Min: 4-6	
No major risk	Max: 8-12	

[a] Conventional water intake, thiazide diuretic use, hospital-acquired hyponatremia of known duration > 48 h.
Information from *Clin J Am Soc Nephrol.* 2024;19:129-135.

(3) Recent guidelines recommend use of bolus dosing over continuous infusion because of its ability to reach target sodium concentrations more quickly and concomitant improvement in Glasgow Coma Scale scores (*Clin J Am Soc Nephrol.* 2024;19(1):129-135).

(b) Prevention of overcorrection with preemptive administration of desmopressin (DDAVP Clamp) (Am J Kidney Dis 2013;61:571-8; *Eur J Endocrinol.* 2014;170(3):G1-47)

(1) Desmopressin 1 to 2 µg intravenously every 6–8 hours + 3% NaCl continuous infusion to achieve a serum sodium increase of 6 mEq/L/day

(2) Not studied with hypertonic saline boluses (evaluated with continuous infusion only)

(3) Only appropriate for severe hyponatremia and high risk of overcorrection

(4) Avoid in patients with heart failure, hepatic cirrhosis, or volume overload

(c) Treatment of overcorrection or relowering of serum sodium is recommended for patients at heightened risk of central pontine demyelination who have their sodium targets overcorrected in the first 24 to 48 hours (*Clin J Am Soc Nephrol.* 2024;19(1):129-135).

(1) Desmopressin 1 to 4 µg intravenously every 8 hours

(2) Free water replacement of 3 mL/kg/hour either enterally with water or parenterally with 5% dextrose in water

(3) Recheck serum sodium every hour and continue until serum sodium goal is achieved

ii. Hypervolemic (ECF expanded) – Fluid and sodium restriction, diuretic therapy as needed. Consider conivaptan or tolvaptan if other therapies fail.

iii. Hypovolemic (ECF reduced) and low urine sodium – Give sodium and fluids for volume expansion (treat etiologies if possible); reduce diuretic therapy. Sodium and fluid administration can be done using 0.9% sodium chloride, lactated Ringer solution, or PlasmaLyte/Normosol intravenously.

iv. Euvolemic (ECF normal) – Consider syndrome of inappropriate antidiuresis or secondary adrenal insufficiency – Fluid restriction first (if clinically appropriate); free water restriction with use of 0.9% sodium chloride solution with or without diuretic therapy. Consider hypertonic saline for acute or severe symptoms. Consider salt tablets, urea, or demeclocycline to maintain normal serum sodium concentrations. Consider conivaptan or tolvaptan if other measures are not effective.

4. Hypernatremia: Reflects a deficit of water compared with total body sodium. Therapy should be adjusted to achieve a serum sodium concentration decrease of 6–8 mEq/L per day; no faster than 10–12 mEq/L per day to reduce the risk of cerebral edema.
    a. Evaluation
        i. Evaluate ECF volume status (increased, normal, decreased). Increased ECF volume is caused by excessive sodium intake (oral salt tablets, hypertonic saline, 0.9% sodium chloride solution, lactated Ringer solution, PlasmaLyte/Normosol). This is the least common cause of hypernatremia. Decreased ECF (hypovolemia, dehydration) results from excessive losses of both water and sodium.
        ii. Consider urine sodium together with volume status to determine cause and treatment.
    b. Treatment
        i. Hypervolemic hypernatremia – Treated with diuretics, sodium restriction, water replacement, and/or renal replacement therapy
        ii. Euvolemic hypernatremia – Treated with free water replacement
            (a) For normal or increased ECF volume, estimate free water deficit with the Adrogue-Madias equation (N Engl J Med 2000;342:1493-9): 0.6 x Wt (kg) x [(serum sodium/140) – 1] (use 0.5 x Wt (kg) for women). Correct deficit over 2–3 days. The equation often underestimates TBW deficit and should only be used a gross estimate for water deficit (Am J Clin Nutr 2013;87:79-85). This is typically accomplished using enteral free water boluses (e.g., 200–300 mL every 4–6 hours) if the patient has a nasogastric feeding or suction tube. Administration of high volumes of enteral water boluses should be avoided if the patient has a post-pyloric tube because it causes cramping and diarrhea. Rare cases of bowel necrosis post–large water boluses have also occurred when administered directly into the small bowel (J Parenter Enteral Nutr 2004;28:27-9). If the enteral route is not possible or the patient is intolerant of enteral water boluses, intravenous dextrose 5% in water or dextrose 5% in 0.225% sodium chloride can be used.
            (b) The anticipated change in serum sodium concentration after 1 L of any intravenous fluid can be estimated as follows: [sodium concentration of IV fluid (mEq/L) – serum sodium concentration (mEq/L)] / [TBW + 1] (N Engl J Med 2000;342:1493-9). Refer to Table 5 for sodium concentration of commonly used intravenous fluids.
        iii. Hypovolemic hypernatremia – Initially treated with volume expansion to restore hemodynamic stability because total body sodium and volume is low. If hypernatremia is still present once the patient is hemodynamically stable, free water replacement can be initiated as stated earlier.
        iv. Clinical evaluation during volume repletion is of paramount importance. Serum sodium should be checked routinely (e.g., every 6–12 hours) to avoid overcorrection. All sources of excess fluid losses should be monitored and replaced with the appropriate fluid, if indicated.

Table 10. Comparative Features of Hypernatremia (Nutr Clin Pract 2008;23:108-21)

ECF Volume Status	Hypervolemic	Euvolemic	Hypovolemic	
Physiologic findings	See Table 6			
Urine sodium (mEq/L)	> 20	Varies	< 20	> 20
Potential etiologies	Excessive sodium intake from intravenous or oral, mineralocorticoid excess	Extrarenal losses (insensible losses), Renal losses (diabetes insipidus)	Extrarenal losses (fever, diarrhea, respiratory losses)	Renal losses (diuretics, glycosuria, kidney failure/injury), diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome

Patient Case

Questions 1–3 pertain to the following case.
A 55-year-old woman (70 kg) admitted to the ICU for pneumonia and respiratory failure develops a serum sodium of 125 mEq/L on her fifth day of hospital admission. Her other laboratory values include a serum potassium of 4.6 mEq/L, chloride (Cl) 100 mEq/L, total carbon dioxide (CO_2) content 24 mEq/L, BUN 20 mg/dL, serum creatinine (SCr) 1.1 mg/dL, and glucose 167 mg/dL. She currently receives a 1-kcal/mL, 62 g of protein/L enteral feeding formula at 60 mL/hour and a 5% dextrose in 0.45% sodium chloride infusion at 25 mL/hour. Her fluid balance has ranged from +300 to +600 mL/day during the past 3 days. She has no evidence of any significant amount of edema. Her measured serum osmolality is 265 mOsm/kg, urine osmolality is 490 mOsm/kg, and urine sodium is 67 mEq/L.

1. Which is the most likely etiology for the patient's hyponatremia?
   A. Factitious hyponatremia
   B. Adrenal insufficiency
   C. Cerebral salt wasting
   D. SIADH

2. Which would be the most appropriate treatment for this woman?
   A. Give sodium chloride tablets 1 g three times daily.
   B. Limit fluids.
   C. Change the intravenous fluid to 0.9% sodium chloride.
   D. Provide a short-term intravenous infusion of 3% sodium chloride.

3. Which change in the enteral feeding formula would be best for this patient?
   A. Add sodium chloride 100 mEq/L to the current formula.
   B. Change the formula to a fish oil–enriched product.
   C. Change the formula to a low-carbohydrate, high-fat product.
   D. Change the formula to a 2-kcal/mL formula, and decrease the rate.

C. Disorders of Potassium Homeostasis
   1. Potassium homeostasis overview
      a. 98% intracellular
      b. Total body stores: 35–50 mEq/kg in normal healthy adults; 25–30 mEq/kg if significantly undernourished
      c. Normal serum concentration: 3.5–5.2 mEq/L
      d. Serum concentration can be influenced by changes in pH (for every 0.1 increase in arterial pH, serum potassium will decrease by around 0.6 mEq/L [range 0.4–1.3 mEq/L]) (*J Am Soc Nephrol.* 2011;22(11):1981-1989), and vice versa. This occurs because of potassium exchanging with hydrogen by the H+/K+-ATPase pump.
      e. Average daily requirement: About 0.5–1.5 mEq/kg
      f. Kidney is primary route of elimination.
      g. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
      h. Magnesium status can influence potassium homeostasis (J Am Soc Nephrol 2007;18:2649-52; Crit Care Med 1996;24:38-45; Arch Intern Med 1992;152:40-5).
         i. Magnesium serves as a cofactor for the Na-K-ATPase pump.
         ii. Magnesium closes potassium channels in distal nephron.

2. Hypokalemia
   a. Definition: Serum potassium less than 3.5 mEq/L, though most ICUs empirically prefer to keep patients at 4.0 mEq/L or greater, if possible.
   b. Signs and symptoms: Weakness, cramps, cardiac arrhythmias (ST depression, QT prolongation, flat T wave, U wave). If severe hypokalemia (e.g., serum potassium less than 2 mEq/L): flaccid paralysis, ileus.
   c. Etiologies:
      i. Inadequate intake (rare; kidneys can usually adapt)
      ii. Increased losses
         (a) GI fluid losses (e.g., diarrhea, fistula, drainages)
         (b) Hypomagnesemia
         (c) Medications (diuretics, amphotericin B, mineralocorticoid excess, cisplatin, extended-spectrum penicillins such as piperacillin, ticarcillin)
         (d) Polyuria (diabetes insipidus)
         (e) Renal potassium excretion (type I/distal and type II/proximal renal tubular acidosis)
         (f) Diabetic ketoacidosis
      iii. Increased requirements (building of new muscle/tissue – refeeding syndrome)
      iv. Extracellular to intracellular shift
         (a) Medications (β-adrenergic agonists, including albuterol, sodium bicarbonate or other alkalinizing agents; insulin)
         (b) Acute alkalemia
         (c) Hypothermia
         (d) Pentobarbital
   d. Treatment:
      i. Treat, alleviate, or reduce the potential etiologies for hypokalemia, if possible.
      ii. Ensure that hypokalemia is not at least partly attributable to hypomagnesemia.
      iii. The estimated deficit should be replaced during a period of 1–3 days (depending on the extent of deficit; the larger the deficit, the longer the repletion period) by giving boluses and increasing the potassium content in intravenous fluids and/or PN formulation.
      iv. Enteral or oral potassium replacement is the preferred and safer route of delivery in asymptomatic patients because of the time of absorption and feed-forward regulation of potassium homeostasis (Ann Intern Med 2009;150:619-25); oral potassium is available in an extended release tablet or capsule (potassium chloride), oral solution (potassium chloride), and effervescent tablet (potassium bicarbonate); the oral solution is limited by poor palatability (preferred for administration via nasogastric/orogastric tube), and bicarbonate salt forms may not be appropriate for patients with a significant metabolic alkalemia; administration of potassium chloride liquid directly into the small bowel (by a jejunal or duodenal feeding tube) should be avoided because of its osmolality, which can lead to abdominal cramping, distension, and diarrhea.
      v. Central administration of intravenous repletion doses of potassium chloride or potassium phosphate is preferred. Potassium chloride can be given at 20 mEq/hour if the patient has continuous electrocardiography (ECG) monitoring. Ten mEq/hour is safest if the patient is asymptomatic.
      vi. Empiric intravenous potassium dosing. Institution or ICU-specific repletion protocols are common and may need to be adjusted according to patient body size, renal function, ongoing losses, and response to previous boluses. The following algorithm is an example of empiric potassium repletion that is based on serum concentrations.

Table 11. Empiric Intravenous Potassium Dosing

Serum Potassium (mEq/L)	Potassium Chloride Dosage (mEq)[a,b]	Laboratory Tests
3.5–3.6	40 to 60 mEq	Obtain BMP, magnesium next AM
3–3.4	80 mEq	Obtain BMP, magnesium next AM; may obtain potassium 1–2 hours after repletion is completed, especially if losses are thought to be high; reassess
2–2.9	120 mEq	Obtain repeat serum potassium 1–2 hours after repletion is completed and reassess; may need one or two additional boluses; repeat; check serum magnesium next AM; reassess

[a] Potassium phosphate may be considered in lieu of potassium chloride if concurrent hypokalemia and hypophosphatemia (very common in critically ill patients receiving EN/PN). Thirty millimoles of potassium phosphate is equivalent to 44 mEq of potassium.

[b] Lower doses may be required for patients with renal dysfunction to avoid overcorrection.

AM = morning; BMP = basic metabolic panel.

vii. The historical assumption of "a 0.5 to 0.6 mEq/L increase in serum potassium will occur for every 40 mEq of intravenous potassium administered" (J Clin Pharmacol 1994;34:1077-82; Arch Intern Med 1990;150:613-7) is potentially inaccurate for many critically ill subpopulations such as emaciated patients or patients with obesity, those with renal dysfunction, exaggerated requirements such as trauma or thermally injured patients (J Parenter Enteral Nutr 2017;41:796-804), those with volume overload, or those receiving diuretic therapy.

viii. Serum potassium concentrations are equilibrated within 1–2 hours after completion of the intravenous potassium chloride infusion (J Clin Pharmacol 1994;34:1077-82; Crit Care Med 1991;19:694-9), and repeated assessments are recommended for patients with severe and/or complicated cases of hypokalemia.

3. Hyperkalemia
   a. Definition: Serum potassium greater than 5.2 mEq/L, although usually not a significant problem until serum potassium approaches 6 mEq/L
   b. Signs and symptoms: ECG changes (peaked and tented T waves) and arrhythmias (bradyarrhythmias, ventricular fibrillation, asystole), symptoms similar to those of hypokalemia (weakness, paralysis)
   c. Etiologies:
      i. Drugs – Potassium-sparing diuretics (spironolactone, amiloride, triamterene), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, heparin, trimethoprim, octreotide, succinylcholine, digoxin
      ii. Excessive intake (usually in combination with compromised renal function) – Be sure to examine all intravenous fluids, EN and PN regimens, penicillin G (1.7 mEq of potassium per million units), packed red blood cells.
      iii. Renal dysfunction (chronic kidney disease [CKD], AKI)
      iv. Hyporeninemic hypoaldosteronism
      v. Tissue catabolism (chemotherapy, rhabdomyolysis, tumor lysis syndrome, crush injury)
      vi. Severe acidemia
      vii. Older adult patients are also at risk because of decreased renal function, reduced renal functional reserve, and loss of body cell mass.
      viii. Laboratory errors (sample hemolysis or improper sample collection)

d. Treatment
   i. The following regimens are for patients with symptomatic evidence of toxicity from hyperkalemia such as peaked T waves on ECG or if serum potassium is greater than 5.5 mg/dL (*Mayo Clin Proc*. 2021;96(3):744-762):

Table 12. Treatment of Hyperkalemia

Stepwise Approach	Mechanism	Treatment	Description
Step 1 - Only if ECG changes	Stabilization of myocardium	Calcium gluconate 10%, 1–2 g IV	Given as slow intravenous push. Repeat dose after 5 minutes if ECG changes persist. Should be given in addition to other therapies as calcium does not affect serum potassium concentration.
		Calcium chloride, 0.5–1 g IV[a]	
Step 2	Intracellular shifting of potassium (temporary redistribution)	Regular human insulin, 10 units IV	Usually given with 1 ampule of D_{50} (25 g). Dextrose can be omitted if the patient has hyperglycemia (BG > 250 mg/dL).
		Sodium bicarbonate, 50–100 mEq IV	Especially useful if patient is acidemic
		Albuterol, 10–20 mg via nebulization over 10 minutes	
Step 3	Elimination of potassium	Loop diuretics	
		Sodium zirconium cyclosilicate (SZC)	Dosed as 10 mg orally every 8 h for up to 48 h, then reassess
		Hemodialysis	The most effective and predictable method for potassium elimination but also the most invasive. Reserved for life-threatening hyperkalemia or for patients already receiving dialysis.

BG = blood glucose; D_{50} = dextrose 50% solution; ECG = electrocardiogram.

[a] Avoid IV push administration of calcium chloride except in cardiac arrest.

   ii. Ensure no exogenous sources of potassium are present (e.g., intravenous fluids, EN, PN); to reduce intake with EN or PN, use a “renal” (no or low-electrolyte) formulation, if necessary.
   iii. Potassium binding agents may be considered in conjunction with standard of care for treatment of acute hyperkalemia (Mayo Clin Proc 2021;96:744-62). Compared with other potassium binders, sodium zirconium cyclosilicate (SZC) has higher selectivity for potassium and the quickest onset of action at 1 hour, which makes it the most favorable option in the acute setting. SZC and patiromer are both more palatable and have superior safety profiles compared with sodium polystyrene sulfate (SPS). The onset of SPS is variable (up to days), as is its efficacy in the acute setting. Additionally, the risk of rare but significant adverse events with the use of SPS, including bowel ischemia, bowel necrosis, and increased hospitalizations, limits its utility as adjunctive therapy for acute hyperkalemia.

D. Disorders of Magnesium Homeostasis
  1. Magnesium homeostasis overview
    a. 99% intracellular (17% of total body content is in the muscle or in the skeleton)
    b. Total body stores: Around 2000 mEq
    c. Normal serum concentration: 1.8–2.4 mg/dL (about 30% bound to protein)
    d. Average daily requirement: Around 24–32 mEq/day
    e. Kidney is primary route of elimination (around 70% reabsorbed in ascending loop of Henle) and is without any hormonal regulation of renal magnesium reabsorption.
    f. Losses can be extensive with severe diarrhea or body fluid drainages (see Table 4).
    g. Magnesium depletion can influence potassium and calcium homeostasis.
  2. Hypomagnesemia
    a. Definition: Although the lower limit of normal for serum magnesium concentrations is 1.8 mg/dL (1.5 mEq/L), most clinicians define significant hypomagnesemia as 1.5 mg/dL (1.3 mEq/L) or less (Annu Rev Med 1981;32:245-59; Nutrition 1997;13:303-8). Many ICUs have a target serum magnesium concentration greater than 2 mg/dL (1.8 mEq/L). Serum concentrations of magnesium may be slightly falsely lowered in the presence of significant hypoalbuminemia (Annu Rev Med 1981;32:245-59; Nutrition 1997;13:303-8).
    b. Signs and symptoms: Muscle weakness, cramping, paresthesias, Chvostek and Trousseau signs, tetany, QT prolongation, hypokalemia, hypocalcemia
    c. Etiologies:
      i. GI losses (especially diarrhea) – Average stool loss of about 6 mEq/L; up to 10–12 mEq/L or greater for secretory diarrheal losses
      ii. Alcohol abuse (increased renal excretion; impaired absorption; poor nutritional status of patients with alcohol use disorder)
      iii. Sepsis/critical illness (increased urinary excretion – several factors)
      iv. Pancreatitis (partly attributable to calcium-magnesium soap formation in peritoneum)
      v. Thermal injury/TBI (increased urinary excretion – several factors)
      vi. Drugs – Diuretics, amphotericin B, caspofungin, cyclosporin/tacrolimus, foscarnet, pentamidine, piperacillin/tazobactam, cisplatin/carboplatin/ifosfamide/cetuximab, lactulose/orlistat, aminoglycosides, and potentially long-term use of digoxin or proton pump inhibitors
      vii. Polyuria (osmotic agents, hypercalcemia, ureagenesis)
    d. Estimating magnesium deficit: For a serum magnesium concentration of less than 1.5 mg/dL (1.3 mEq/L), a 1- to 2-mEq/kg deficit can be expected.
    e. Treatment:
      i. Treat the etiology (if possible). Be sure to treat magnesium deficiency at the same time or before potassium therapy if the patient is also hypokalemic.
      ii. Successful treatment of hypomagnesemia usually takes 4–5 days of intravenous therapy. Intramuscular magnesium therapy for replacement therapy is inadvisable given the limit on volume per injection site with respect to dosage requirements and tissue irritation.
      iii. Intravenous magnesium sulfate 32–48 mEq/day (4–6 g/day) – Suggested to be sufficient to maintain serum magnesium within 2–2.5 mg/dL for most magnesium-deficient patients (Crit Care Med 1996;24:38-45; Annu Rev Med 1981;32:245-59)

iv. Empiric intravenous magnesium sulfate dosing. This algorithm (Table 13) was designed primarily for trauma and thermally injured patients but can likely be universally applied to other critically ill patient populations (Nutrition 1997;13:303-8). The therapy may need to be adjusted according to renal function and ongoing severity of losses. An empiric approach to dosing intracellular electrolytes for patients with significant renal impairment is to give one-half the recommended dose. However, electrolyte therapy for patients with renal impairment must be individualized according to patient response. Certain patient populations, such as those with cholinergic disorders, may be harmed with administration of magnesium sulfate; hence, an adequate patient history is paramount for patient safety.

v. Magnesium concentrations are often elevated for several hours or longer after an infusion because it takes about 48 hours for the magnesium to fully redistribute to the body tissues (Nutrition 1997;13:303-8). One-time repletion doses are usually not adequate for large deficits, and levels should continue to be monitored daily to ensure an appropriate assessment of magnesium is made after redistribution of previous bolus doses.

Table 13. Empiric Intravenous Magnesium Sulfate Dosing

Serum Magnesium (mg/dL)	Dose (g/kg)[a]
1.6–1.8	0.05
1–1.5	0.1
< 1	0.15

[a] For ease of use and preparation, intravenous magnesium sulfate should be ordered in 2-g increments (e.g., 2 g, 4 g, 6 g). The drug should be mixed in 50-100 mL of normal saline or 5% dextrose and given at a rate no faster than 1 g (8 mEq) per hour (Nutrition 1997;13:303-8). Commercially available sources of magnesium sulfate are available in 2 gram/50 mL and 4 mEq/100 mL premixed bags. Maximum dose should be held at a ceiling of 8–10 g per administration. Intravenous magnesium may be administered by the peripheral or central venous route.

vi. Oral magnesium: It can be difficult to successfully replenish magnesium if given by the oral route in critically ill patients because of the adverse GI effects of oral magnesium (e.g., diarrhea) and the high elemental magnesium doses required to achieve repletion. Although it has been inferred that certain oral magnesium products are better tolerated than others (e.g., gluconate vs. oxide), this tolerability likely pertains to the elemental magnesium content of the products. The lower the elemental magnesium content, the more tolerable the oral product. However, the lower the magnesium content, the more difficult it is to achieve magnesium repletion for a patient with significant magnesium depletion. Oral magnesium replacement is a reasonable option for patients who are asymptomatic and tolerating oral intake as long as their magnesium concentration is not below 1 mg/dL.

Table 14. Common Oral Magnesium Products

Salt Form	Strength (mg)	Elemental Magnesium Content (mEq)	Usual Dosing
Oxide	400 140	19.8 6.9	1–2 tablets two or three times daily
Gluconate	500	2.2	1–2 tablets two or three times daily
Chloride	520	2.6	1–2 tablets two or three times daily

Table 15. Oral Magnesium Content

Salt Form	% Elemental Magnesium Content
Oxide	60
Carbonate	45
Hydroxide	42
Citrate	16
Lactate	12
Chloride	12
Sulfate	10
Gluconate	5

3. Hypermagnesemia
   a. Definition: Serum magnesium concentration greater than 2.4 mg/dL
   b. Signs and symptoms: Hypotension, decreased deep tendon reflexes, cardiovascular manifestations (e.g., bradycardia, somnolence, muscle paralysis, arrhythmias) generally do not occur until serum concentrations are greater than 4 mg/dL.
   c. Etiologies: Renal failure or impairment, early post-infusion elevation of serum magnesium concentration, excessive dosing of magnesium/antacids, post-cathartic use (e.g., magnesium citrate) – To develop hypermagnesemia, these events usually occur together with renal impairment.
   d. Treatment:
      i. Remove source of magnesium intake.
      ii. Intermittent slow bolus doses of calcium gluconate (2 g) for 5–10 minutes until severe symptoms abate (the effect of calcium is transient, and repeat therapy may be needed as often as every hour). The effects of magnesium on neuromuscular and cardiac function are antagonized by calcium.
      iii. Ventilate the patient, if necessary.
      iv. 0.9% sodium chloride infusion with loop diuretic therapy
      v. Hemodialysis

Patient Case

Questions 4 and 5 pertain to the following case.
A 65-year-old man (weight 87 kg) is admitted to the hospital with severe acute pancreatitis. A computed tomography (CT) scan of the abdomen reveals a pancreatic pseudocyst. He is to remain NPO (nothing by mouth) because of marked abdominal pain on a low-fat diet and during a trial of EN; therefore, he is given PN. He is a 2 pack/day tobacco smoker and has a history of frequent alcohol consumption. His serum laboratory values are as follows: sodium (Na) 139 mEq/L, potassium (K) 3.3 mEq/L, Cl 102 mEq/L, total CO_2 content 25 mEq/L, BUN 14 mg/dL, SCr 0.8 mg/dL, calcium 7.6 mg/dL, phosphorus 2.2 mg/dL, magnesium 1.5 mg/dL, and albumin 2.5 g/dL.

4. Which potassium-phosphorus dosing regimen would be most appropriate for this patient?
    A. Potassium phosphate 30 mmol intravenously x 1 dose, followed by potassium chloride 40 mEq via NG tube x 2 doses.
    B. Potassium phosphate 30 mmol intravenously x 1 dose, followed by potassium chloride 40 mEq intravenously x 1 dose.
    C. Potassium phosphate 60 mmol intravenously x 1 dose.
    D. Potassium chloride 40 mEq via NG tube x 2 doses, followed by Neutra-Phos 250 mg via NG tube x 2 doses.

5. In addition to potassium and phosphorus supplementation, the patient is given magnesium sulfate 6 g intravenously for 6 hours. His repeat serum magnesium the next day is 2.0 mg/dL. Which therapeutic option would be best for this patient?
    A. Give magnesium oxide 500 mg twice daily for the next few days.
    B. Give magnesium sulfate 2–4 g intravenously daily for the next few days.
    C. Give an additional dose of 8 g of magnesium sulfate intravenously.
    D. No additional treatment is necessary.

E. Disorders of Calcium Homeostasis
  1. Calcium homeostasis overview
    a. Most prevalent intracellular cation in body; 99% of body's calcium is in bone; highly protein bound in plasma
    b. Total body stores: About 1–1.2 kg of calcium
    c. Normal serum concentration: 8.5–10.5 mg/dL; normal serum ionized concentration 1.12–1.32 mmol/L
    d. Serum concentration can be influenced by:
      i. Changes in plasma albumin concentration – For every 1 g/dL in serum albumin below 4 g/dL, serum calcium will decrease by around 0.8 mg/dL (Clin Chim Acta 1971;35:483-9). This estimation of serum calcium concentrations is inaccurate in critically ill patients and should not be used (JPEN J Parenter Enteral Nutr 2004;28:133-41). Ionized calcium concentrations should be used for assessing calcium in critically ill patients. However, most critically ill patients (85%) with a total serum calcium concentration less than 7 mg/dL are hypocalcemic (ionized serum calcium of 1.12 mmol/L or less) (Nutr Clin Pract 2007;22:323-8).
      ii. Changes in pH (for every 0.1-unit increase in arterial pH, serum ionized calcium will decrease by about 0.05 mmol/L) (Arch Pathol Lab Med 2002;126:947-50) because of increased protein binding

   e. Average daily requirement: 10–15 mEq/day intravenously with PN (Ann Surg 1983;197:1-6); 1–3 g/day orally
   f. Kidney is primary route of elimination.
   g. Magnesium status can influence calcium homeostasis (J Parenter Enteral Nutr 2004;28:133-41; Annu Rev Med 1981;32:245-59).
      i. Hypomagnesemia results in end-organ resistance to parathyroid hormone.
      ii. Hypomagnesemia may impair parathyroid hormone secretion.
      iii. Hypocalcemia will correct within 2 days after hypomagnesemia is corrected.
2. Hypocalcemia
   a. Definition: Corrected serum total calcium less than 8.5 mg/dL (non-ICU patients); ionized serum calcium concentration less than 1.12 mmol/L
   b. Signs and symptoms: Tingling, paresthesias, hyperactive deep tendon reflexes, tetany (Chvostek and Trousseau signs), seizures, prolonged QT interval
   c. Etiologies
      i. Critical illness, surgery
      ii. Continuous renal replacement therapy (CRRT) and citrate anticoagulation
      iii. Massive blood transfusion (citrate in packed RBCs)
      iv. Hypomagnesemia
      v. Hyperphosphatemia
      vi. Pancreatitis
      vii. Drugs (amphotericin B, cisplatin, cyclosporine, foscarnet, bisphosphonates, loop diuretics, sodium bicarbonate, cinacalcet, fluoride poisoning)
      viii. Malabsorption
      ix. Hypoparathyroidism, hypothyroidism
      x. CKD/AKI
      xi. Vitamin D deficiency
      xii. Severe alkalemia
   d. Treatment: See Table 16 for an empiric algorithm for intravenous repletion of calcium. (JPEN J Parenter Enteral Nutr 2007;31:228-33; JPEN J Parenter Enteral Nutr 2005;29:436-4; Nutrition 2007;23:9-15).

Table 16. Empiric IV Calcium Dosing[a-e]

Ionized Calcium (mmol/L)	Calcium Gluconate	Calcium Chloride Dosing
1–1.12	2 g (9.3 mEq) of in 100 mL for 2 hours	0.67 g (9.4 mEq) in 100-mL solution over 1 h
≤ 0.99	4 g (18.6 mEq) of calcium gluconate in 100 or 250 mL for 4 hours	1.3 g (18.2 mEq) in 100 mL over 1 h

[a] Calcium gluconate is the preferred method of repletion. Calcium chloride should be used (preferably) only in code situations, not for routine replacement therapy, because the chloride salt contains about 2.5 times the amount of elemental calcium and can cause tissue necrosis when given peripherally in contrast to calcium gluconate. In addition, calcium chloride should never be added to the PN solution unless there is no phosphate in the PN solution and the commercial amino acids used in the PN solution do not contain phosphorus (some amino acid products do contain phosphate). A serum ionized calcium concentration determination should be repeated several hours after completing the calcium infusion to allow equilibration (Nutrition 2007;23:9-15). More aggressive therapy may need to be considered for patients with tetany or life-threatening cardiac arrhythmias caused by hypocalcemia.

[b] Intravenous calcium administration should be used with extreme caution in patients with severe hypokalemia or in those receiving digoxin or other digitalis alkaloids.

[c] Always check the serum phosphorus concentration because hyperphosphatemia can induce hypocalcemia, given the metastatic precipitation of calcium phosphate in the soft tissues and lungs (usually associated with renal disease).

[d] Both calcium preparations are compatible with 0.9% NaCl and D5W.

[e] Use of a continuous infusion of calcium may be considered in some situations where severe and/or persistent hypocalcemia may occur. Examples include during continuous renal replacement therapy and massive transfusion protocols where there may be concern for citrate-related toxicity. In these cases, 4 g of calcium gluconate or chloride can be added to 1 L of solution and initiated at 50-100 mL/h. Further titrations should be made on the basis of repeat calcium concentrations (*Endocr Connect*. 2019;8(6):X1).

D5W = 5% dextrose in water; NaCl = sodium chloride.

Patient Case

Questions 6 and 7 pertain to the following case.
A 24-year-old man (weight 90 kg) is admitted to the trauma ICU postoperatively from repair of his duodenal, jejunal, ileal, and colon injuries; hepatorrhaphy; and splenectomy after several gunshot wounds to the abdomen. He also received 10 units of packed red blood cells. He has a serum ionized calcium concentration of 0.86 mmol/L, K 4.6 mEq/L, and magnesium 1.8 mg/dL. His SCr concentration is 0.8 mg/dL, and his urine output is 0.5 mL/kg/hour.

6. Which is the most likely etiology of his hypocalcemia?
   - A. Hypomagnesemia
   - B. Excessive urinary diuresis
   - C. Blood transfusion
   - D. Critical illness

7. Which therapeutic regimen would be best for this patient?
   - A. Calcium gluconate 2 g intravenously for 2 hours
   - B. Calcium gluconate 4 g intravenously for 4 hours
   - C. Calcium chloride 1 g intravenous push for 5–10 minutes
   - D. No calcium therapy necessary.

3. Hypercalcemia
   - a. Definition: Corrected serum calcium greater than 10.5 mg/dL or ionized calcium greater than 1.32 mmol/L; signs and symptoms are more evident when total serum calcium of 12 mg/dL or greater or ionized calcium of 1.5 mmol/L or greater.
   - b. Signs and symptoms: Mental status changes, polyuria, shortened QT interval, bradycardia, atrioventricular block
   - c. Etiologies:
     - i. Immobilization
     - ii. Chronic critical illness–associated metabolic bone disease
     - iii. Excessive calcium intake
     - iv. Hyperparathyroidism
     - v. Granulomatous diseases (tuberculosis, sarcoidosis)
     - vi. Malignancy
     - vii. Drugs (thiazide diuretics, vitamin D, lithium, teriparatide)
     - viii. Dehydration
     - ix. Thyrotoxicosis
     - x. Adrenal insufficiency
   - d. Treatment:
     - i. Mobilize the patient (if possible); discontinue calcium supplementation
     - ii. Intravenous fluids with 0.9% sodium chloride (if dehydrated) at 200–300 mL/hour x 48 hours or until rehydrated with or without furosemide 40–80 mg intravenously every 12 hours

  - iii. Calcitonin 4 units/kg intramuscularly or subcutaneously every 12 hours; can be increased to a maximum of 8 units/kg every 8 hours. Calcitonin inhibits bone reabsorption and promotes the renal excretion of calcium by decreasing tubular reabsorption. The onset of action is rapid (within hours); however, tachyphylaxis can occur because of down-regulation of calcitonin receptors within days (J Intensive Care Med 2015;30:235-52) so duration of use should be limited to 24–72 hours. Calcitonin is most useful in patients with symptomatic hypercalcemia in combination with rehydration.
  - iv. Bisphosphonates.
    - (a) Pamidronate
      - (1) 30 mg intravenously daily × 3 days if the cause is immobilization or chronic critical illness–associated metabolic bone disease
      - (2) 90 mg intravenously × 1 for other causes
    - (b) Zoledronic acid is an option; however, evidence in chronic critical illness–associated metabolic bone disease is lacking.
    - (c) Onset of action for hypercalcemia is typically at least 48 hours.
    - (d) Use caution in renal impairment.
    - (e) Redosing bisphosphonates may be considered, but the frequency of such varies depending on etiology (*Chest.* 2000;118(3):761-766).
  - v. Denosumab is preferred in patients with bisphosphonate-refractory hypercalcemia or those with poor kidney function (JAMA 2022;328:1624-36). Although it is not renally excreted, the degree of kidney impairment that warrants the use of denosumab over other options for hypercalcemia is not clearly established. Further, the presence of kidney dysfunction increases the risk of hypocalcemia from denosumab; therefore, a single dose of 60 mg or 0.3 mg/kg subcutaneously may be used in patients with kidney disease or in bishphosphonate-naive patients with moderate hypercalcemia. Otherwise, doses up to 120 mg once weekly for 3 weeks can be used. If the etiology of hypercalcemia persists, then 120 mg can continue to be administered every 4 weeks starting 2 weeks after the initial 3 weekly doses.
  - vi. Parathyroidectomy for patients with primary hyperparathyroidism. If surgery is not an option, cinacalcet may be used for patients with severe, chronic hypercalcemia from hyperparathyroidism (JAMA 2022;328:1624-36).
  - vii. Prednisone 40 mg/day and greater for 10 days for patients with granulomatous diseases (e.g., sarcoidosis, tuberculosis)
  - viii. Hemodialysis may be necessary for severe hypercalcemia (serum calcium greater than 3 mmol/L).

F. Disorders of Phosphorus Homeostasis
  1. Phosphorus homeostasis overview
    - a. 99% intracellular, of which 85% is bound to bone
    - b. Extracellular pool of phosphorus: Around 600 mg (about 20 mmol), 10% protein bound
    - c. Normal serum concentration: 2.5–4.5 mg/dL
    - d. Serum concentration can be influenced by parathyroid hormone (increased parathyroid hormone leads to increased urinary excretion of phosphorus), and alkalemia can decrease serum phosphorus concentration.
    - e. Average daily requirement: Around 20 mg/kg/day
    - f. Kidney is primary route of elimination.
  2. Hypophosphatemia
    - a. Definition: Serum phosphorus less than 2.5–3 mg/dL; severe hypophosphatemia less than 1 mg/dL

b. Signs and symptoms: Weakness, paresthesias; severe depletion can lead to congestive cardiomyopathy, cardiac arrest, seizures, coma, respiratory arrest due to weakness of the diaphragm, rhabdomyolysis

c. Etiologies:
   - i. Alcoholism
   - ii. Malnutrition/refeeding syndrome
   - iii. Critical illness (especially trauma, TBI, thermal injury)
   - iv. Diabetic ketoacidosis
   - v. Hepatic resection
   - vi. Drugs – Insulin, catecholamines, antacids, sucralfate, calcium, ferric carboxymaltose injection, diuretics
   - vii. Alkalemia
   - viii. Malabsorption – Chronic diarrhea
   - ix. Hyperparathyroidism
   - x. Cancer (phosphatonins [e.g., fibroblast growth factor-23])
   - xi. Renal replacement therapies
   - xii. Hungry bone syndrome following parathyroidectomy or thyroidectomy

d. Treatment
   - i. Target serum phosphorus concentration when patient is in the ICU and ventilator dependent: About 4 mg/dL (Intensive Care Med 1995;21:826-31; N Engl J Med 1985;313:420-4)
   - ii. Intravenous dosing guidelines

Table 17. Intravenous Phosphorus Dosing Guidelines[a,b]

Serum Phosphorus (mg/dL)	General Medical-Surgical Population Dosage (mmol/kg) (Crit Care Med 1995;23:1504-11)	High Requirements[c] Population Dosage (mmol/kg) (JPEN J Parenter Enteral Nutr 2006;30:209-14)
2.3–3	0.16	0.32
1.6–2.2	0.32	0.64
< 1.6	0.64	1

[a] The drug should be mixed in 100–250 mL of normal saline or 5% dextrose in water and given at a rate no faster than 7.5 mmol/hour. Phosphorus should always be ordered in millimoles for ease of use and preparation. For ease of use and preparation in the pharmacy, phosphorus should be ordered in units divisible by 3 mmol (e.g., 15, 30, 45, 60) whenever possible.

[b] Potassium phosphate salt can be used for patients with a serum potassium less than 4 mEq/L, but ensure potassium content does not exceed estimated potassium repletion needs (for most products, 3 mmol of phosphorus = 4.4 mEq of potassium; for one commercially-available product, 3 mmol of phosphorus = 4.7 mEq of potassium). Sodium phosphate salt should be used for patients with a serum potassium of 4 mEq/L or greater or if the potassium content of potassium phosphate dose would exceed potassium repletion needs (3 mmol of phosphorus = 4 mEq of sodium).

[c] Patients with thermal injury (JPEN J Parenter Enteral Nutr 2001;25:152-9), those with trauma (especially those with a traumatic brain injury) (Nutrition 2010;26:784-90; JPEN J Parenter Enteral Nutr 2006;30:209-14), those malnourished with evidence of significant complications from refeeding syndrome, or those with hepatic resections.

   - iii. Repletion using oral phosphorus formulations
     - (a) Oral phosphorous replacement is not recommended for cases of severe hypophosphatemia because of the need to rapidly correct the phosphorous concentration and the potential for adverse effects (eg, diarrhea) with higher oral doses. A recent study evaluated the usefulness of oral phosphorous replacement in critically ill patients with mild to moderate hypophosphatemia and found no difference in efficacy with a reduction in waste and cost (*Crit Care Med*. 2024;52(7):1054-1064).
     - (b) Oral phosphorous preparations are widely available, but differences exist in the amount of phosphorous, potassium, and sodium each product contains.

3. Hyperphosphatemia
    a. Definition: Serum phosphorus concentration greater than 5 mg/dL, usually not clinically relevant until serum phosphorus is greater than 6 mg/dL
    b. Signs and symptoms: Hypocalcemia and metastatic calcification (e.g., neuromuscular irritability, prolonged QT interval, tetany) – Usually does not occur until the serum calcium-phosphorus product approaches 55 mg/dL or greater (Adv Exp Med Biol 1978;103:195-201).
    c. Etiologies:
        i. Renal failure
        ii. Immobility
        iii. Chronic critical illness–associated metabolic bone disease
        iv. Excessive phosphorus intake
        v. Vitamin D toxicity
        vi. Tumor lysis syndrome
        vii. Hypoparathyroidism
    d. Treatment:
        i. Reduce phosphorus intake (omit from PN solution, with or without reduction of ILE content of PN solution if a high-fat formulation [controversial as phosphorus in organic form: phospholipids and not inorganic such as sodium phosphate]; change to “low- or no-electrolyte” renal enteral formula).
        ii. Phosphate binders if consuming oral/enteral nutrition (EN) (Am J Health Syst Pharm 2005;62:2355-61). Dosing should be timed with meals for patients consuming oral diets or given at regular intervals before and/or during enteral nutrition administration for patients on EN.

Table 18. Phosphate Binders

Drug	Available Strength	Phosphorus-Binding Capacity	Recommended Empiric Initial Dose
Calcium carbonate[a]	500, 750, 1000 mg per tablet	Calcium 43 mg/g	1 g QID
Calcium acetate[a]	667 mg per tablet	Calcium 106 mg/g	1334–2001 mg TID
Sevelamer[b]	400 mg, 800 mg per tablet; 800 mg or 2400 mg per packet (for oral suspension)	Sevelamer 80 mg/g	800–1600 mg TID
Lanthanum[c]	500, 750, 1000 mg per tablet or packet	Lanthanum 78–156 mg/g	500 mg TID
Ferric citrate[d]	210 mg per tablet	Iron 84.8-87.9 mg per gram and Citrate 19.1-19.8 mg per gram	420 mg TID
Sucroferric oxyhydroxide[d]	500 mg per tablet	Sucroferric 260 mg per gram	500 mg TID

[a] Do not use if the patient is hypercalcemic.

[b] Sevelamer carbonate comes in a powder for suspension; easier for administering to patients receiving EN; less likely to worsen metabolic acidosis than tablet in patients with renal failure because tablet is in hydrochloric acid salt form.

[c] 750 and 1000 mg available as oral packet; 500, 750, and 1000 mg available as chewable tablet.

[d] May increase iron concentrations.

EN = oral/enteral nutrition; QID = four times daily; TID = three times daily.

II. ACID-BASE DISORDERS

A. Normal Homeostasis
   1. Normal values

Table 19. Normal Blood Gas Values

Variables	Arterial Blood	Mixed Venous Blood
pH	7.35–7.45	7.31–7.41
P_{CO_2}	35–45	41–51
P_{O_2}	80–100	35–40
HCO_3	22–26	22–26
Base excess	-2 to +2	-2 to +2
O_2 saturation	> 95%	70%–75%

HCO_3 = bicarbonate.

2. Interpreting ABGs
   a. Acidemia (pH less than 7.35) versus alkalemia (pH greater than 7.45)
   b. Acidemia and alkalemia refer to serum pH being either low or high, respectively. Acidosis and alkalosis refer to the metabolic or respiratory processes that led to the abnormal pH. Although the terms *emia* and *osis* are similar, they are different.
   c. For simple acid-base disorders, identify pH, P_{CO_2}, and HCO_3 in that order. Whichever side of 7.40 the pH is on, the respiratory or metabolic processes that coincide with that pH abnormality are the primary etiology. If the pH is less than 7.40, an elevated P_{CO_2} (respiratory acidosis) or a decreased HCO_3 (metabolic acidosis) is the primary etiology. If the pH is greater than 7.40, a decreased P_{CO_2} (respiratory alkalosis) or an increased HCO_3 (metabolic alkalosis) is the primary etiology. An easy introductory overview to acid-base disorders by Haber is provided in the references (West J Med 1991;155:146-51).
   d. Sometimes more than one primary abnormality is present, or the anticipated compensatory process (metabolic or respiratory) is inadequate and may be contributing to the acid-base disorder. As a result, various formulas have been developed to predict what may be considered adequate compensation. However, these mathematical equations have limitations in their clinical utility and accuracy (J Trauma Acute Care Surg 2012;73:27-32; Clin J Am Soc Nephrol 2007;2:162-74; Crit Care Med 2007;35:1264-70; Am J Respir Crit Care Med 2000;162:2246-51; Arch Intern Med 1992;152:1625-9; J Crit Care 2013;28:1103; N Engl J Med 2014;371:1434-45) and can be difficult to memorize (West J Med 1991;155:146-51).
   e. Mixed acid-base disorders are more nuanced to interpret in patients with non–steady-state conditions and in those receiving mechanical ventilation, which provides exogenous respiratory compensation. Some of the more common equations for assessing acid-base disorders are discussed later in this chapter.

Box 1. Adverse Effects of Severe Acidemia (pH 7.25 or less)

Impaired cardiac output
Increased metabolic demands
Peripheral ischemia (centralization of blood)
Insulin resistance and hyperglycemia
Increased pulmonary vascular resistance
Decreased ATP synthesis
Hypotension
Increased protein breakdown
Increased risk of arrhythmias
Hyperkalemia
Decreased catecholamine responsiveness
Diaphragmatic fatigue/dyspnea
Obtundation/coma
Hyperventilation

Box 2. Adverse Effects of Severe Alkalemia (pH of 7.55 or greater)

Arteriolar constriction
Hypokalemia
Hypotension
Hypophosphatemia
Increased risk of arrhythmias
Hypocalcemia/tetany
Decreased coronary blood flow/decreased angina threshold
Organic acid production
Seizures
Hypoventilation/hypercapnia/hypoxemia
Lethargy, delirium, stupor

3. Use of base excess
   a. Reflects the amount of base needed in vitro to return the plasma pH to 7.40 at standard conditions ($P\mathrm{CO}_2$ 40 mm Hg, body temperature 37°C)
   b. Base excess reflects the metabolic component to interpreting the ABG. Despite its simplicity, it has limitations (J Trauma Acute Care Surg 2012;73:27-32). Crystalloid resuscitation (leading to hyperchloremic acidosis), exogenous bicarbonate (HCO_3) administration, ethanol ingestion, and acetate/HCO_3 buffer in hemodialysis or CRRT solutions can lead to erroneous base excess calculations and errors in interpretation (J Trauma Acute Care Surg 2012;73:27-32).
4. Compensatory response to acid-base disorders

Table 20. Anticipated Compensation to Acid-Base Disorders

Primary Disorder	Serum Bicarbonate (mEq/L)	Anticipated $P\mathrm{CO}_2$ (mm Hg)
Metabolic acidosis	< 22	$(1.5 \times HCO_3) + 8\ (\pm 2)$
Metabolic alkalosis	> 26	$(0.7 \times HCO_3) + 20$

Table 20. Anticipated Compensation to Acid-Base Disorders (*Continued*)

Primary Disorder		P_{CO_2} (mm Hg)	Anticipated Serum Bicarbonate (mEq/L)
Respiratory acidosis	Acute[a]	> 42	HCO_3 should increase by 1 mEq/L for every 10 mm Hg increase in P_{CO_2} above 40 mm Hg
	Chronic[a]		HCO_3 should increase by 4–5 mEq/L for every 10 mm Hg increase in P_{CO_2} above 40 mm Hg
Respiratory alkalosis	Acute[a]	< 38	HCO_3 should decrease by 2 mEq/L for every 10 mm Hg decrease in P_{CO_2} below 40 mm Hg
	Chronic[a]		HCO_3 should decrease by 4–5 mEq/L for every 10 mm Hg decrease in P_{CO_2} below 40 mm Hg

[a]Compensation is different for acute versus chronic respiratory disorders because it takes about 2 days for the kidneys to adapt to a persistent change in respiratory status.

Information from: Berend K, de Vries APJ, Gans ROB. Physiological approach of acid-base disturbances. N Engl J Med 2014;371:1434-45.

B. Respiratory Acidosis
   1. Common causes include pulmonary edema, pulmonary embolism, pneumonia, CNS depression, cardiac arrest, stroke, spinal cord injury, excessive sedation/analgesia, and overfeeding with PN/EN.
   2. Metabolic compensation – See Table 20.

C. Respiratory Alkalosis
   1. Common causes include uncontrolled pain, nicotine and drug withdrawal, agitation, pneumonia, stimulant drugs, salicylate toxicity (due to direct respiratory stimulation), and head injury.
   2. Metabolic compensation – See Table 20.

D. Metabolic Acidosis
   1. Use of the serum anion gap (AG)
      a. Used to determine the etiology for the metabolic acidosis. AG is the difference between major cations and anions in blood (trying to detect whether there is an abundance of unmeasured anions). If an AG is present, then a metabolic acidosis is present, regardless of pH or HCO_3.

$$AG = Na – (Cl + HCO_3)$$

      b. Normal range is about 3–14 mEq/L. Some clinicians will include serum potassium when calculating cations (and the normal AG will need to be adjusted), but this is uncommon.
      c. Adjust AG for serum albumin (Crit Care Med 1998;26:1807-10). The difference in serum albumin concentration (grams per deciliter) from normal should be multiplied by 2–2.5 and added to the anions (chloride and bicarbonate).

$$\text{Albumin adjusted AG} = Na - Cl - HCO_3 - (2.5 \times [4 - \text{serum albumin}]).$$

      Some clinicians also adjust for serum phosphorus (Crit Care Med 2007;35:2630-6). Serum phosphorus (milligrams per deciliter) can be multiplied by 0.5 and added to anions, and lactate can also be included but is not common in routine clinical practice. Using this method (and including serum potassium), the adjusted AG (or sometimes called the strong ion gap when referring to the physicochemical methodology for interpreting acid-base disorders) should be close to 0 (± 2) if the patient does not have an AG acidosis.

d. Causes of an AG acidosis: One easy pneumonic to remember (there are others) is MUDPILES:
M = Methanol
U = Uremia (including rhabdomyolysis)
D = Diabetes (diabetic ketoacidosis [DKA]*) *Incidence of euglycemic DKA has grown with increase in use of sodium-glucose transporter 2 inhibitors.
P = Paraldehyde, propylene glycol
I = Isoniazid or iron
L = Lactic acidosis
E = Ethylene glycol or ethanol toxicity
S = Salicylates

e. Types of lactic acidosis (lactate greater than 4 mmol/L and pH less than 7.35)
   i. Type A: Hypoperfusion (cardiogenic or septic shock, regional ischemia, severe anemia)
   ii. Type B: Metabolic – No tissue hypoxia
      (a) B1 = underlying disease (diabetes, liver disease, leukemia, lymphoma, AIDS)
      (b) B2 = drugs/toxins (metformin, didanosine/stavudine/zidovudine, ethanol, linezolid, propofol, propylene glycol toxicity caused by intravenous lorazepam or pentobarbital), nitroprusside (cyanide) toxicity
      (c) B3 = inborn errors of metabolism (pyruvate dehydrogenase deficiency)

f. Causes of a normal AG acidosis
Another easy pneumonic to remember (there are others) is ACCRUED.
A = Ammonium chloride/acetazolamide (urine bicarbonate loss)
C = Chloride intake (PN, intravenous solutions)
C = Cholestyramine (GI bicarbonate loss)
R = Renal tubular acidosis: Types I, II, and IV
U = Urine diverted into the intestine (e.g., ileal conduit, vesicoenteric fistula)
E = Endocrine disorders (e.g., aldosterone deficiency)
D = Diarrhea or small/large bowel fluid losses (e.g., enterocutaneous fistulas)

2. In the presence of an elevated AG, the delta ratio can be assessed for determining mixed acid-base disorders
Delta ratio =
$\Delta AG/\Delta HCO_3$ = (measured AG − normal AG)/(normal HCO_3 − measured HCO_3) =
(AG−14)/(24 − measured HCO_3)

Table 21. Interpreting Delta Ratio[a]

Delta Ratio	Assessment
< 0.4	Hyperchloremic normal AG acidosis
< 1	Mixed high AG acidosis and hyperchloremic normal AG acidosis
1–2	AG acidosis (no hidden process)
> 2	High AG acidosis and concurrent metabolic alkalosis OR a preexisting compensated respiratory alkalosis

[a] The ratio should be used cautiously in interpreting mixed acid-base disorders, given that it is associated with poor sensitivity because of several influencing factors (J Am Soc Nephrol 2007;18:2429-31). This author prefers to look at current clinical state/diagnoses and recent therapeutic interventions for the patient to ascertain whether a mixed acid-base disorder is potentially present.

3. An alternative method (and perhaps a simpler approach) to the delta ratio is to calculate the "excess gap" compared with the AG (West J Med 1991;155:146-51).
   Excess gap = AG – 14.
   a. The excess gap is then added to the measured serum bicarbonate concentration.
   b. If the sum is less than a normal serum bicarbonate concentration (e.g., 28–30 mEq/L), a mixed AG and non-AG acidosis is present.
   c. If the sum is greater than a normal HCO_3 concentration, the patient likely has an AG acidosis and concurrent metabolic alkalosis.
4. Evaluation of respiratory compensation: See Table 20.
5. Treatment
   a. Aggressive interventional therapy unnecessary until pH less than 7.20–7.25
   b. Treat primary etiology! This should be the focus of treating the acid-base disorder.
   c. Intravenous sources of alkali – Done conservatively in conjunction with treating primary disorder whenever possible. The intent is not to normalize the pH but to improve the pH (definitely avoid overcorrection).
      i. Sodium bicarbonate – Most commonly used
      ii. Sodium acetate – Available in PN solutions and compounded intravenous fluids
      iii. Sodium citrate – Used orally for patients with chronic kidney injury
   d. Total bicarbonate dose (mEq) = 0.5 x Wt (kg) x (24 - HCO_3)
      i. Give one-third to one-half of the calculated total dose (or 1–2 mEq/kg) for several hours to achieve a pH of around 7.25 (avoid boluses if possible).
      ii. Once the pH is around 7.25 or greater, slower correction without increasing bicarbonate more than 4–6 mEq/L to avoid exceeding the target pH
      iii. Serial ABGs (e.g., every 6 hours); watch rate of decrease in serum potassium and calcium
      iv. Use of sodium bicarbonate injection is controversial in patients with lactic acidosis (Curr Opin Crit Care 2008;14:379-83).
      v. The BICAR-ICU study (Lancet 2018;392:31-40) evaluated 389 critically ill patients with metabolic acidemia in a multicenter, intention-to-treat trial in which patients were randomized to sodium bicarbonate therapy or placebo. Most patients had an elevated serum lactate at enrollment. The primary outcome (composite of death by day 28 and presence of at least one organ failure at day 7) was not statistically significant. However, in the prespecified stratum of patients with AKI, the primary outcome was decreased in the treatment group (37% vs. 54%, p=0.0283).
   e. Adverse effects of excess sodium bicarbonate:
      i. Hypernatremia, hyperosmolality, volume overload
      ii. Hypokalemia, hypocalcemia, hypophosphatemia
      iii. Paradoxical worsening of the acidosis (if the fractional increase in Pco_2 production exceeds the fractional bicarbonate change)
      iv. Over-alkalinization

Patient Case

Questions 8 and 9 pertain to the following case.
A 60-year-old woman (weight 80 kg) was admitted to the hospital after 1 week of severe diarrhea. She presents with clinical evidence of dehydration (hypotension, tachycardia, decreased urine output) and is weak. Her serum laboratory values are as follows: Na 145 mEq/L, K 3.0 mEq/L, Cl 118 mEq/L, total CO_2 18 mEq/L, BUN 29 mg/dL, SCr 0.9 mg/dL, glucose 122 mg/dL, calcium 9.1 mg/dL, phosphorus 3.7 mg/dL, magnesium 1.4 mg/L, albumin 3.9 g/dL, and lactate 1.6 mmol/L. Her ABG is pH 7.29, Po_2 93 mm Hg, Pco_2 34 mm Hg, HCO_3 17 mEq/L, and base excess -5 mEq/L. She has a 30 pack/year smoking history.

8. Which best describes the patient's type of acid-base disorder?
   A. Hyperchloremic, normal AG acidosis
   B. AG acidosis
   C. AG acidosis with hyperchloremia
   D. Respiratory alkalosis with concurrent metabolic alkalosis

9. Which is the most appropriate initial fluid therapy for this patient?
   A. 0.45% sodium chloride with potassium chloride 20 mEq/L
   B. 0.9% sodium chloride with potassium chloride 20 mEq/L
   C. Lactated Ringer solution
   D. 5% dextrose

E. Metabolic Alkalosis: pH greater than 7.45; symptoms are not usually severe until pH is greater than 7.55–7.60.
   1. Assessment (to help guide treatment) based on urinary chloride
      a. Saline responsive (urinary chloride less than 10 mEq/L)
         i. Excessive gastric fluid losses
         ii. Diuretic therapy (especially loop diuretics)
         iii. Dehydration (contraction alkalosis)
         iv. Hypokalemia
         v. (Over-) Correction of chronic hypercapnia
      b. Saline resistant (urinary chloride greater than 20 mEq/L)
         i. Excessive mineralocorticoid activity (e.g., hydrocortisone, fludrocortisone, licorice)
         ii. Excessive alkali intake
         iii. Profound potassium depletion (serum potassium less than 3 mEq/L)
         iv. Massive blood transfusion
      c. Respiratory compensation (highly variable and may not be possible for ventilator-dependent patients)
      d. Intravascular volume status (important for saline-responsive alkalemia)
   2. Treatment – Saline-responsive alkalemia
      a. Treat underlying cause (if possible).
      b. Decreased intravascular volume: Give intravenous 0.9% sodium chloride, Plasmalyte/Normosol, or Lactated Ringer's infusion (with potassium chloride, if necessary).
      c. Increased intravascular volume: Acetazolamide 250–500 mg orally or intravenously once to four times daily plus potassium chloride if necessary (Intensive Care Med 2010;36:859-63; Crit Care Med 1999;27:1257-61; Acta Anaesthesiol Scand 1983;27:252-4).
         i. Hydrochloric acid therapy if alkalosis is refractory or initial pH greater than 7.6
            (a) 0.1 N or 0.2 N of hydrochloric acid (use 0.2 N for patients requiring fluid restriction). Hydrochloric acid should be given by central venous administration, and the solution must be in a glass bottle.

- ii. Dosage of hydrochloric acid:
  - (a) Chloride deficit (Arch Surg 1975;110:819-21):
    Dose (mEq) = 0.2 L/kg x Wt (kg) x (103 − serum chloride)
  - (b) Bicarbonate excess (J Am Soc Nephrol 2000;11:369-75):
    Dose (mEq) = 0.5 L/kg x Wt (kg) x (serum bicarbonate -24)
  - (c) A practical approach is to administer one-half of the calculated dose over 12 hours and repeat the arterial blood gas at 6 and 12 hours with readjustment of infusion rate, if necessary. Discontinue the infusion when the pH is less than 7.5.

3. Treatment – Saline-unresponsive alkalosis: Treat underlying cause (if possible).
   - a. Exogenous corticosteroids – Decrease dose or use drug with less mineralocorticoid effect.
   - b. Excessive alkali intake – Alter regimen.
   - c. Profound hypokalemia (serum potassium less than 3 mEq/L) – Aggressive potassium supplementation
   - d. Rare causes: Endogenous mineralocorticoid excess (Bartter or Gitelman syndrome) – Spironolactone, amiloride, or triamterene; consider surgery
   - e. Liddle syndrome: Amiloride or triamterene

III. NUTRITION SUPPORT

A. Nutritional Assessment
1. Nutrition Risk Assessment
   - a. "Determination of Nutrition Risk" – recommended by 2016 SCCM/ASPEN guidelines to guide the approach to nutrition support therapy in critically ill patients. High nutrition risk identifies those patients most likely to benefit from early EN therapy. (JPEN J Parenter Enteral Nutr 2016;40: 159-211)
     - i. Nutritional Risk Screening (NRS 2002; Clin Nutr 2003;22:321-36)

Table 22. Determination of Nutrition Risk by NRS 2002 score

Nutritional Status		**Severity of Disease**	
	Score		**Score**
Normal Nutritional Status	0	Normal nutritional requirements	0
Wt loss > 5% in 3 months or food intake < 50% to 70% of normal in preceding week	1	Hip fracture, chronic patients with acute complications (e.g., cirrhosis, COPD, diabetes, oncology)	1
Wt loss > 5% in 2 months or body mass index (BMI) 18.5 to 20.5 + impaired general condition or food intake < 25% to 50% of normal in preceding week	2	Major abdominal surgery, stroke, pneumonia, hematologic malignancy	2
Wt loss > 5% in 1 month (~15% in 3 months) or BMI < 18.5 + impaired general condition or food intake 0 to 25% of normal in preceding week	3	Head injury, bone marrow transplantation, critically ill ICU patient	3
Add the two scores (nutritional status + severity of disease). If age 70 years or greater, add 1 to total score. If age-corrected score 3 or greater, start nutritional support.			

ii. Nutrition Risk in the Critically Ill (NUTRIC) score (Crit Care 2011;15:R268)

Table 23. Determination of Nutrition Risk by the NUTRIC Score

Variable	Range	Points
Age, yrs	< 50 50 - 74 > 74	0 1 2
APACHE II	< 15 15 -19 20 - 28 > 28	0 1 2 3
SOFA	< 6 6 – 9 > 9	0 1 2
Number of comorbidities	0 - 1 > 1	0 1
Days from hospital to ICU admission	0 - < 1 ≥ 1	0 1
IL-6	0 - < 400 ≥ 400	0 1
High Score = 6 to 10 points: Associated with worse clinical outcomes and are most likely to benefit from aggressive nutrition therapy Low Score = 0 to 5 points: These patients have a low nutrition risk		

iii. Modified NUTRIC Score (Clin Nutr 2016;35:158-62). Because IL-6 is not routinely available for assessment, a modified NUTRIC (mNUTRIC) score has been validated, which omits IL-6. An mNUTRIC score of 5 or greater is considered high nutrition risk.

2. Malnutrition categories
   a. American Society for Parenteral and Enteral Nutrition (ASPEN) International Consensus Nomenclature (JPEN J Parenter Enteral Nutr 2010;34:156-9)
      i. Starvation-related malnutrition (e.g., anorexia nervosa)
      ii. Chronic disease-related malnutrition (e.g., inflammatory bowel disease, organ failure)
      iii. Acute disease or injury-related malnutrition (e.g., major infection, burns, trauma)
   b. “Classic” definition – Not in favor with conventional assessment techniques and tools
      i. Marasmus (e.g., decreased fat/muscle protein stores but normal serum proteins)
      ii. Kwashiorkor (e.g., normal fat, decreased muscle protein, and serum proteins)
      iii. Kwashiorkor-Marasmus mix (decreased fat, muscle protein, and serum proteins)
   c. Based on body mass index (BMI) = weight (kg)/height^2 (m^2) – Should not be used alone to identify malnutrition
      i. Less than 18.5 kg/m^2: Underweight
      ii. 18.5–24.9 kg/m^2: Normal
      iii. 25–29.9 kg/m^2: Overweight
      iv. 30–34.9 kg/m^2: Class I obesity
      v. 35–39.9 kg/m^2: Class II obesity
      vi. Greater than 40 kg/m^2: Class III obesity

d. Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition Consensus Malnutrition Characteristics (JPEN J Parenter Enteral Nutr 2012;36:275-83)
    i. Diagnosed by the presence of two or more of the following:
        (a) Insufficient energy intake
        (b) Weight loss
        (c) Loss of muscle mass
        (d) Loss of subcutaneous fat
        (e) Localized or generalized fluid accumulation (may sometimes mask weight loss)
        (f) Diminished functional status as measured by hand grip strength
            (1) In the context of these criteria, hand grip strength intended to be used to document decline in physical function as appropriate to patient circumstances
    ii. Nonsevere (moderate) or severe malnutrition determined by duration and severity of above symptoms, which is further categorized as:
        (a) Acute illness or injury-related malnutrition
        (b) Chronic disease-related malnutrition
        (c) Social or environmental-related malnutrition
    iii. Visceral protein concentrations (e.g., albumin, prealbumin, transferrin) are not reliable indicators and not included in this definition. They should not be used to assess nutrition status in critically ill patients (JPEN J Parenteral Enteral Nutr 2016;40:159-211; Nutr Clin Pract 2021;36:22-8).
    iv. BMI is not included in this classification because patients become malnourished regardless of body habitus.

3. Empiric weight adjustment for amputations (Table 24)

Table 24. Body Compartments' Contribution to Body Weight (J Am Diet Assoc 1995;95:215-8)

Body Part Amputation	Approximate Contribution to Body Weight (%)
Foot	1.5
Calf, foot	5.9
Leg (from hip)	16
Hand	0.7
Hand and forearm	2.3
Arm	5

B. Energy Requirements

Assessing caloric requirements: Indirect calorimetry – Measured energy expenditure by oxygen consumption and CO_2 production – The "gold standard"

1. Respiratory quotient ($V{CO_2}/V{O_2}$); 1 for carbohydrate oxidation; 0.7 for fat oxidation; 0.8 for protein oxidation; greater than 1 usually implies overfeeding (net fat synthesis), less than 0.7 suggests ketosis or an error in measurement (too much fraction of inspired oxygen [$F{IO_2}$] variability at higher $F{IO_2}$ concentrations). Widespread use in clinical practice is limited by availability and cost of indirect calorimeters. Furthermore, accuracy of measurements is affected by many common factors in the ICU (presence of chest tubes, use of supplemental oxygen, FiO_2 settings, PEEP settings, CRRT, anesthesia, movement).
2. Organization guideline recommendations

Table 25. Guideline Recommendations for Caloric Intake[a]

Organization	Recommendation
Eastern Association for Surgery of Trauma (*J Trauma*. 2004;57:660-669)	22-25 kcal/kg/d for patients with paraplegia 20-22 kcal/kg for patients with quadriplegia
SCCM/ASPEN (*JPEN J Parenter Enteral Nutr.* 2016;40:159-211)	25-30 kcal/kg/d or use of indirect calorimetry (lower amounts may be administered to medical ICU patients with ARDS for the first week) Obesity: Goal EN regimen should not be > 65%-70% target energy requirements as measured by indirect calorimetry. For BMI 30-50 kg/m^2, a weight-based equation of 11-14 kcal/kg actual body weight/d is recommended. For BMI > 50 kg/m^2, 22-25 kcal/kg ideal body weight/d is recommended
ASPEN (*JPEN J Parenter Enteral Nutr.* 2022;46:12-41)	In the first 7-10 days of ICU stay, 12-25 kcal/kg/d (recommended because of no findings of significant difference in clinical outcomes between patients with higher vs lower intake; however, this does not take into account nutrition risk, presence of malnutrition, ICU patient population [most supporting literature is in medical ICU], or that most patients receiving EN will receive substantially less than goal intake during this time because of frequent interruptions to feeding for ICU care)
ESPEN (*Clin Nutr.* 2023;42:1671-1689)	20-25 kcal/kg/d (in the absence of measured REE)

[a] Actual body weight is used for all calculations except where otherwise specified.

ARDS = acute respiratory distress syndrome; ASPEN = American Society for Parenteral and Enteral Nutrition; BEE = basal energy expenditure; EN = enteral nutrition; ESPEN = European Society for Clinical Nutrition and Metabolism; REE = resting energy expenditure; SCCM = Society of Critical Care Medicine.

3. Predictive methods
    a. Mifflin-St. Jeor equations (preferred for non–ventilator-dependent patients with obesity, AKI or CKD, or hepatic encephalopathy when a hypocaloric, high-protein regimen is not possible)
        i. Women = (10 x Wt) + (6.25 x Ht) – (5 x Age) − 161*
        ii. Men = (10 x Wt) + (6.25 x Ht) − (5 x Age) + 5*
        *Age (years); Ht (centimeters); Wt = actual body weight (kilograms).
    b. Penn State equation (preferred for ventilator-dependent patients with obesity):
    REE = (Mifflin x 0.96) + (Tmax x 167) + (Ve x 31) − 6212*
    *REE = resting energy expenditure; Tmax = maximum temperature in degrees Celsius; Ve = minute ventilation, liters per minute.
    c. Modified Penn State equation (preferred for ventilator-dependent patients with obesity 60 years or older
    REE = (Mifflin x 0.71) + (Tmax x 85) + (Ve x 64) − 3085*
    d. Basal energy expenditure (BEE) – Harris-Benedict equations (preferred for small adults and older adult patients)
        i. Women = 655 + (9.6 x Wt) + (1.7 x Ht) − (4.7 x Age)*
        ii. Men = 66 + (13.7 x Wt) + (5 x Ht) − (6.8 x Age)*
        *Wt (kilograms), Ht (centimeters), Age (years).

4. Adverse effects of overfeeding – Do not exceed 4–5 mg/kg/minute of glucose/carbohydrate in the acute phase of critical illness (Ann Surg 1979;190:274-85); limit total caloric intake (do not exceed 1.3–1.5 x measured REE or 25–30 kcal/kg/day for most patients); do not exceed soybean oil (SO)-ILE intake of 2.5 g/kg/day; most clinicians limit SO-ILE in critically ill patients to around 1 g/kg/day or less.
    a. Hypercapnia: It was traditionally thought that excessive glucose intake alone was responsible for hypercapnia observed during overfeeding. However, studies of acutely ill patients showed that aggressive feeding resulted in marked increases in CO_2 production (Ann Surg 1980;191:40-6; JAMA 1980;243:1444-7). Substitution of glucose kilocalories with lipid decreases CO_2 production (Anesthesiology 1981;54:373-7) when overfeeding but does not alter CO_2 production if not overfeeding (e.g., 1.3 x BEE) (Chest 1992;102:551-5). Because most institutions lack the ability to measure energy expenditure, estimates are used. If the patient experiences hypercapnia without a known cause, the nutrition therapy should be suspected and the caloric intake empirically decreased (especially if the patient is having difficulty weaning from the ventilator).
    b. Hyperglycemia: In a retrospective study of 102 patients receiving PN and who were not predisposed to hyperglycemia, dextrose intakes in excess of 5 mg/kg/minute resulted in substantial hyperglycemia (blood glucose [BG] greater than 200 mg/dL) in 18 of 37 patients (Nutr Clin Pract 1996;11:151-6). Patients with stress-induced hyperglycemia or diabetes are even more susceptible to hyperglycemia with EN or PN. This is one reason (of many) that critically ill patients who require PN should receive PN via continuous infusion rather than cyclic infusion (i.e., over 12–14 hour/night), even if they tolerated a cyclic infusion of PN prior to ICU admission (Nutr Clin Pract 2023;38:1263-72).
    c. Fatty infiltration of the liver: May be because of overfeeding with fat or carbohydrate. Usually presents as a cholestatic liver disease (increased gamma-glutamyl transferase (GGT), alkaline phosphatase, and ultimately bilirubin) after at least 1 week to 10 days of overfeeding (Arch Surg 1978;113:504-8). May be transient or reversible or can progress to end-stage liver disease. Throughout a few weeks, patients can appear jaundiced. Patients with critical illness and/or infections tend to be more susceptible to hepatic steatosis compared with non–critically ill patients (possibly because of an exaggerated inflammatory process). Although treatment with fish oil appears promising in infants and children (Nutr Clin Pract 2013;28:30-9; Ann Surg 2009;250:395-402), data for adults are limited. Usual treatment for adult patients with suspected PN-associated liver disease is first to ensure that the patient is not being overfed. Although evidence is lacking, most nutrition support clinicians would agree that if 100% SO-ILE is being used, consideration of an ILE formulation with a lower percentage of SO is warranted (refer PN formulation section for description of ILE formulations). Cyclic PN (when PN is infused over fewer hours per day) may be considered for patients who are no longer critically ill. However, cyclic PN is typically not appropriate for critically ill patients due to the high glucose infusion rate and large volumes of fluid (relative to time) required for administration. Reinstituting EN as soon as possible (if possible) is of utmost importance.

C. Protein Requirements
    1. Guideline recommendations

Table 26. Guideline Recommendations for Protein Intake[a]

Organization	Recommendation
SCCM/ASPEN (JPEN J Parenter Enteral Nutr. 2016;40:159-211)	1.2-2 g/kg/d; higher amounts are likely needed for multiple trauma or burns; higher amounts are needed during continuous renal replacement therapy (CRRT), up to 2.5 g/kg/d For patients with open abdomen, provide an additional 15-30 g of protein per liter of output from wound drain(s) or negative-pressure wound devices (caused by exposure of peritoneum, which produces high-protein exudate)
International Protein Summit consensus recommendations (*Nutr Clin Pract*. 2017;32(suppl 1):142S-151S)—in reference to ICU patients	BMI < 30 kg/m^2: 1.2-2 g/kg/d ABW 1.2 g/kg/d Obesity (BMI 30-39.9 kg/m^2): 2 g/kg IBW/d Obesity (BMI ≥ 40 kg/m^2): 2.5 g/kg IBW/d AKI: 1.2-2 g/kg/d Age > 60 y: 2-2.5 g/kg/d Persistent inflammation catabolism syndrome: 1.2-2 g/kg/d Infants and children: A minimum of 1.5 g/kg/d
ASPEN 2022	No recommendations for protein beyond 2016 recommendations—see row 1
ESPEN ICU (*Clin Nutr.* 2023;42:1671-1689)	1.3 g/kg/d

[a]Actual body weight should be used for calculations, except where otherwise specified.

ABW = adjusted body weight; AKI = acute kidney injury; ASPEN = American Society for Parenteral and Enteral Nutrition; ESPEN = European Society for Clinical Nutrition and Metabolism; IBW = ideal body weight; SCCM = Society of Critical Care Medicine.

2. Does more protein really make a difference?
    a. Weijs et al. (2012) (JPEN J Parenter Enteral Nutr 2012;36:60-8): 28-day mortality improved in those who received an average of 1.3 g/kg/day versus 1.1 or 0.8 g/kg/day (886 mixed ICU patients).
    b. Allingstrup et al. (2012) (Clin Nutr 2012;31:462-8): 28-day mortality improved in those who received an average of 1.5 g/kg/day versus 1.1 or 0.8 g/kg/day (113 mixed ICU patients).
    c. JPEN J Parenter Enteral Nutr 2016;40:45-51: Improved survival with protein intake greater than 80% of goal (1.2 g/kg/day) in 2828 mixed ICU patients. Achieving 80% of caloric goals did not affect mortality.
    d. Crit Care Med 2017;45:156-63: Mortality was decreased with increased protein intake for high-risk (NUTRIC score greater than 4) mixed ICU patients with a prolonged ICU stay of more than 11 days. Low-risk patients were unaffected.
    e. ASPEN guidelines for nutrition support in adult critically ill patients (2022) (JPEN J Parenter Enteral Nutr 2022;46:12-41): Based on the low number of high-quality trials available for evaluation, no difference in clinical outcomes has been observed with provision of higher versus lower protein intake.
    f. EFFORT Protein Trial (2023) (Lancet 2023;401:568-576): No difference in incidence of alive at hospital discharge between patients who received an average protein intake of 1.6 versus 0.9 g/kg/day (high protein versus usual dose protein, respectively). Subgroup analyses on alive at discharge and 60-day mortality favored usual dose protein group for patients with AKI (1301 mixed ICU patients, 83.6% study population in medical ICU).

D. Principles of EN and PN
1. Indications for EN: If the patient is unable to eat adequate amounts to achieve goal nutritional intake. EN is preferred to PN because EN helps maintain the integrity of the GI tract, has fewer infectious complications, is associated with decreased ICU length of stay, and is more cost-effective (JPEN J Parenter Enteral Nutr 2009;33:277-316; Ann Surg 1992;215:503-13; JPEN J Parenter Enteral Nutr 2016;40:159-211). This position has been challenged recently because of newer literature (JAMA 2013;309:2130-8; Lancet 2013;381:385-93; N Engl J Med 2014;371:1673-84; Crit Care 2016;20:117; Clin Nutr 2017;36:623-50) indicating a reduction in infectious complications with PN as compared with the past literature (likely because of improvements in catheter care, PN formula management and compounding practices, and glycemic control standards over the past several decades). In fact, the 2022 ASPEN guidelines for critically ill patients recommends that either PN or EN is acceptable as the primary feeding modality in the first week of critical illness (evidence GRADE: high; strength of GRADE recommendation: strong) (JPEN J Parenter Enteral Nutr 2022;46:12-41). This is based on findings that similar energy intake provided as PN is not superior to EN and no differences in harm were shown. Patient-specific factors and clinical judgment should guide the choice between PN versus EN.
   a. Lack of bowel sounds, flatus, or bowel movement is not a contraindication for EN because these are nonspecific indicators of GI function (JPEN J Parenter Enteral Nutr 2009;33:277-316; SCCM/ASPEN 2009).Evidence of ileus (e.g., dilated loops of bowel on abdominal radiography) is, however, a relative contraindication for EN.
   b. High NG output (greater than around 800 mL NG output) in a 24-hour period may indicate delayed gastric emptying, and the patient may not be ready for EN when fed into the stomach and post-pyloric feeding is not possible. High NG output may also indicate an ongoing ileus or obstruction, in which case, PN may be indicated, especially if at high nutrition risk.
   c. Refusal to eat/anorexia is not an absolute contraindication for EN. Ensure appropriate dietary preferences, and add high-calorie/protein liquid supplements to meals and bedtime snack first.
2. EN formulas

Table 27. EN Formulas

Product Category	Indication	Macronutrients	Additional Comments	Examples
Standard tube feeding	Minimal stress	1–1.2 kcal/mL Protein 40–50 g/L	Polymeric, 300–500 mOsm/kg, fiber	Jevity, Nutren 1.0, Fibersource HN
Volume restricted	Congestive heart failure, fluid-restricted patients	2 kcal/mL Protein 60–80 g/L	Polymeric, 700–800 mOsm/kg, fiber	Nutren 2.0, Resource 2.0, TwoCal HN
Renal	AKI (predialysis), renal dysfunction with increased serum potassium, phosphorus, magnesium	2 kcal/mL Protein 30–40 g/L	High calorie, low protein, no or low electrolytes, 600 mOsm/kg, volume restricted, fiber	Renalcal, Suplena
Renal	Renal failure with hemodialysis	1.8–2 kcal/mL Protein 80–90 g/L	High calorie, modest electrolytes, volume restricted, 1000 mOsm/kg, fiber	Novasource Renal, Nepro

Table 27. EN Formulas (*Continued*)

Product Category	Indication	Macronutrients	Additional Comments	Examples
Increased protein needs	Critically ill patients (especially trauma, surgical, burns)	1 kcal/mL Protein 62 g/L	High-protein content, fiber, isotonic	Replete, Promote
Glucose intolerance	Hyperglycemia, diabetes	1.2 kcal/mL Protein 60 g/L	Low-carbohydrate content, fiber	Diabetisource AC, Glucerna 1.2
Immune enhancing	Critically ill surgical and trauma patients, perioperative GI cancer	1.5 kcal/mL Protein 90–94 g/L	Additional arginine, glutamine; fish oil	Impact Peptide 1.5, Pivot
Bariatric	Patients with obesity with good renal function	1 kcal/mL Protein 93 g/L	High protein, low calories	Peptamen Intense VHP
Elemental	Malabsorption, fat intolerance	1–1.5 kcal/mL Protein 50–68 g/L	Low fat/MCT, di/tri-peptides/free AA, no fiber, low residue	Vivonex RTF, Vital
Protein supplement	High protein needs	10–15 g of protein per serving is typical (products vary)	Protein liquid, gel, or powder	Pro-Stat, ProMod

AA = amino acids; MCT = medium-chain triglycerides.

3. Enteral nutrition – Medication interactions: Hold EN 1 hour before and after drug administration. *Increase EN rate to account for time off EN.
   a. Warfarin (Pharmacotherapy 2008;28:308-13)
   b. Phenytoin (Nutr Clin Pract 1996;11:28-31)
   c. Levothyroxine (J Endocrinol Invest 2014;37:583-7; Nutr Clin Pract 2010;25:646-52) - In one study, liquid levothyroxine preparation was shown to alleviate need to hold EN. In lieu of holding EN, increasing the levothyroxine dose by 25 mcg per day with weekly monitoring of thyroid function tests has also been described. Care should be taken to reduce the dose back to the patient's home dose when they are transitioned off of EN if this option is chosen.
   d. Itraconazole (Antimicrob Agents Chemother 1997;41:2714-8)
   e. Fluoroquinolones (J Antimicrob Chemother 1996;38:871-6)
   *Some clinicians have empirically increased the dosage of these drugs while giving continuous enteral feeding rather than holding the EN for 1 hour before and after drug administration. With the exception of levothyroxine, this author discourages this practice, especially for warfarin and phenytoin, because the doses necessary to overcome the effects of drug binding to the continuous EN are potentially toxic when the EN is held or discontinued without a dose adjustment. Others have increased the ciprofloxacin dose to 750 mg twice daily during continuous EN to achieve therapeutic plasma concentrations well above the MIC (minimum inhibitory concentration) for a gram-negative urinary tract infection (J Antimicrob Chemother 1996;38:871-6).

    f. Vasopressors (*Lancet Respir Med*. 2023;11(7):602-612; *J Clin Nutr*. 2023;42(9):1671-1689). Use of EN while patients are receiving vasopressors is controversial because of the potential for intestinal ischemia and necrosis from reduced blood flow to the GI tract. Given the known benefits of early nutrition in critically ill patients, balancing the use of EN in this population is important. The NUTRIREA-3 trial confirmed that early EN (within 24 hours of intubation) with hypocaloric feeds (defined as 6 kcal/kg/d and 0.2-0.4 g/kg/d of protein) in patients receiving median vasopressor doses of 0.5 μg/kg/min reduced duration of ICU status and adverse GI-related events without significantly reducing mortality. EN should generally be avoided/delayed in uncontrolled shock but should be initiated as soon as shock has stabilized and vasopressor doses are no longer escalating.

4. Indications for PN
    a. European Society for Clinical Nutrition and Metabolism (ESPEN) ICU guidelines (2023) (Clin Nutr 2023;42:1671-89): When oral nutrition and EN are contraindicated, PN should be initiated within 3–7 days in critically ill patients. Early PN (within 48 hours) can be provided instead of no nutrition if contraindications to EN are present in patients who are severely malnourished or at high nutrition risk.
    b. SCCM/ASPEN (2016) (JPEN J Parenter Enteral Nutr 2016;40:159-211) It is recommended to initiate PN as soon as possible after intensive care unit (ICU) admission if patients have contraindications to EN and are severely malnourished or at "high nutrition risk" as indicated by the NRS 2002 or NUTRIC score. PN should be avoided in the acute phase of sepsis regardless of the degree of nutrition risk because studies show longer hospital and ICU stays, longer duration of organ support, higher incidence of infectious complications, and higher hospital mortality with early supplemental and/or exclusive PN (JPEN J Parenter Enteral Nutr 2016;40:159-211). See a recent review on the controversial role of supplemental PN in adult patients (Nutr Clin Pract 2018;33:359-69).
    c. Other possible indications for PN: Severe, intractable vomiting or diarrhea, obstruction, impaired absorption (e.g., short bowel syndrome, high ostomy output), high-output enterocutaneous fistula (more than 500 mL/day), ischemic bowel, bowel discontinuity (JPEN J Parenter Enteral Nutr 2017;41:324-77)
    d. Summary: The approach depends on several factors (e.g., if the patient is malnourished or well nourished before ICU admission, patient acuity). Early nutrition (defined as within 24–72 hours according to published studies) appears to be beneficial for those with prolonged ICU stays and a high level of catabolism, including trauma, TBI, and thermal injury and for some surgical subpopulations. Impact of early nutrition appears more variable with respect to clinical outcome for medical ICU patients and is likely related to a shorter duration in ICU stay and a lower level of catabolism for many patients. Recent literature supports the safe use of PN as a substitute for EN (when EN is contraindicated or when EN delivery is inadequate) with no difference in the incidence of infections.
5. PN formulations
    a. Peripheral versus central venous administration
        i. Osmolarity of PN admixtures for peripheral administration is limited to less than 900 mOsm/L.
        ii. Because of osmolality restrictions, peripheral PN solutions are "diluted," requiring large volumes (contraindicated for fluid-restricted patients and difficult for older patients) and typically do not allow for adequate protein and energy provision.
        iii. Phlebitis is common with peripheral PN and it is difficult to use beyond 2–3 days in most types of peripheral access.
        iv. A central PN formulation should be delivered into a line with the catheter tip ending in a large diameter vein, such as the distal superior vena cava, adjacent to the right atrium. Central PN formulations are generally preferred for critically ill patients who require PN.

b. Safe practice recommendations for prescribing PN solutions – Should be prescribed in total amount per day (e.g., dextrose 200 g/day, “brand X” amino acids 150 g/day, “brand Y” lipids 50 g/day, fluid volume 1800 mL/day, sodium chloride 60 mEq/day, potassium acetate 80 mEq/day), NOT by concentrations (e.g., 20% dextrose, 8% amino acids) or by compounding techniques (e.g., 500 mL of 50% dextrose in water plus 500 mL of 10% amino acids). Because different brands of amino acids and ILEs contain different ingredients and have different compatibility and stability profiles, the brand name of these ingredients should also be noted in the PN prescription and label (JPEN J Parenter Enteral Nutr 2014;8:296-333).

c. Glucose requirements
   i. Obligatory requirements for CNS, renal medulla, bone marrow, leukocytes, etc.: Around 130 g/day
   ii. Surgical wound healing requires about 80–150 g/day (based on atrioventricular differences and blood flow from a burned limb)
   iii. Caloric contribution of glucose: 3.4 kcal/g (as opposed to carbohydrate 4 kcal/g)
   iv. Mean glucose oxidation rate in critically ill patients is around 5 mg/kg/day (or about 25 kcal/kg/day as glucose). In general, most clinicians avoid exceeding this glucose intake in the acute phase of critical illness.

d. ILE requirements
   i. SO-ILE products have historically been the main source of ILE in the United States. ILE may be given separately from the PN admixture or as part of the PN solution. When given separately from the dextrose/amino acid formulation, the maximum allowable hang time according to the FDA is 12 hours. Previous recommendations were to consider withholding SO-ILE during the first week following initiation of PN in critically ill patients (or limiting to 100 g/week during this time) (JPEN J Parenter Enteral Nutr 2016;40:159-211). This is due to the high omega-6 fatty acid (more pro-inflammatory) content of SO-ILE and limited evidence suggesting worse outcomes for ICU patients who receive ILE early in their ICU course. However, this evidence is very limited with several notable design flaws that likely confounded study outcomes (J Trauma 1997;43:52-60). Several ILE products are now commercially available in the United States, but owing to the limitations of available evidence, the 2022 ASPEN guidelines for nutrition support in critically ill patients do not make a recommendation for one ILE product over another. SMOFlipid consists of 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil (OO), and 15% fish oil (FO). It may be more advantageous than 100% SO-ILE because of a decreased propensity to cause elevated serum triglyceride concentrations and decreased exposure to SO without compromising caloric intake. Additionally, limited data analyses suggest decreased infections in ICU patients and decreased liver function tests with prolonged PN use. Daily administration is usually required to meet essential fatty acid requirements (met only by the SO component). A 100% FO-ILE product is also FDA-approved for use in pediatric patients in the United States, and an OO,SO-ILE product (80% OO, 20% SO) is also approved for use in adults. All clinical and practical considerations listed previously should be evaluated when choosing which ILE product to use for critically ill patients.
   ii. Caloric contribution of ILE 10% = 1.1 kcal/mL (11 kcal/g); 20% = 2 kcal/mL (10 kcal/g); 30% = 3 kcal/mL (10 kcal/g)
   iii. Dosage: About 100–150 g of soybean oil weekly (or 1–1.5 g/kg weekly) is enough to prevent essential fatty acid deficiency (EFAD). The FDA states a maximum upper limit of 2.5 g/kg/day in adults, though SO-ILE provision in critically ill patients should generally be maintained at less than 1 g/kg/day. The recommended dosing for SMOFlipid is 1–2 g/kg/day, and OO,SO-ILE formulations can be provided at doses of 1–1.5 g/kg/day. However, EFAD requirements can be met with SMOFlipid doses as low as 12.6% and OO,SO-ILE formulations as low as 12-25% of total calories. (Nutr Clin Pract 2020;35:769-82).

iv. Biochemical evidence for EFAD (the "classic definition" is an increased triene/tetraene [eicosatrienoic acid/arachidonic acid] ratio greater than 0.2) occurs in 30%, 66%, 83%, and 100% of patients after 1, 2, 3, and 4 weeks of fat-free "full-calorie, continuous" PN (Surgery 1978;84:271-7). Clinical signs and symptoms of EFAD (dry, scaly skin; hair loss; poor wound healing) usually do not occur until about 2 weeks after biochemical evidence in adults. Therefore, in most adults, the earliest appearance of EFAD is after about 3 weeks of fat-free full-calorie continuous PN. Because the investigators initiated ILE soon after the biochemical appearance of EFAD, only 2 of 32 patients developed clinical evidence suggestive of EFAD. EFAD can occur much sooner for infants and children. Patients with obesity receiving hypocaloric high-protein therapy can maintain normal plasma fatty acid profiles for up to 5 weeks (J Nutr Biochem 1994;5:243-7). Cyclic PN has been suggested to mobilize lipid from endogenous depots, but conclusive data are lacking and cyclic PN should be avoided in critically ill patients, as previously discussed.

v. Serum triglyceride concentration should be monitored at least weekly and more often for those with proven or suspected impaired triglyceride clearance (consider temporarily withholding lipid emulsion when serum triglyceride approaches or exceeds 400 mg/dL) (Nutr Clin Pract 2020;35:769-82).

vi. Predisposing conditions that may result in impaired clearance of triglycerides:
  (a) Excessive lipid intake (propofol and clevidipine are 2 drugs commonly used in the ICU setting that contain lipids within their preparation. Propofol is a 10% emulsion containing 1.1 kcal/mL, and clevidipine is a 20% emulsion containing 2 kcal/mL)
  (b) Acute pancreatitis
  (c) Uncontrolled diabetes
  (d) Liver failure
  (e) Kidney failure (decreased lipoprotein lipase activity, carnitine deficiency with long-term hemodialysis patients)
  (f) End-stage sepsis (multisystem organ failure)
  (g) History of hyperlipidemia
  (h) Obesity
  (i) HIV (occurred even before current antiretroviral therapy) (Am J Med 1989;86:27-31)
  (j) Pregnancy
  (k) Small-for-gestational-age neonates (carnitine synthesis is maturational-dependent)

e. Electrolyte requirements (see the Fluids and Electrolytes section)
  i. When initiating nutrition, particularly in patients with prolonged malnutrition and at high nutrition risk, the occurrence of profound electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypophosphatemia) typically reflects refeeding syndrome. To prevent refeeding syndrome, consider initiating nutrition at hypocaloric doses and titrating toward goal over 1 to 3 days. If a patient experiences refeeding syndrome, recommendations are to slow the rate of feeding and aggressively replete electrolytes according to guideline recommendations.

f. Vitamins
  i. One full dose of multiple vitamins for infusion (i.e., 10 mL/day) should be included in every bag of PN with few exceptions.
  ii. Conservative supplementation doses (i.e., higher than basal needs to replace losses) of certain vitamins may be safely added to most PN admixtures (e.g. thiamine or folic acid).
  iii. Repletion doses of vitamins (i.e., to correct a known deficiency) should be provided separately from the PN admixture because of numerous possible interactions affecting compatibility and stability of the admixture (JPEN J Parenter Enteral Nutr 2022;46:273-99).

g. Trace minerals

i. Zinc 3 mg/day normal requirements; 5 mg/day during critical illness; increased requirements for patients with diarrhea, intestinal fistulae. An additional 10 mg/day for a total of 13 mg/day is usually sufficient to meet increased intestinal losses (Gastroenterology 1979;76:458-67). Deficiency is characterized by loss of hair; erythematous rash, especially in periorbital regions of face; poor wound healing. Classic zinc deficiency is termed *acrodermatitis enteropathica*.

ii. Copper 0.3–0.5 mg/day is usually sufficient (Gastroenterology 1981;81:290-7). Historically, copper deficiency was considered to be a rare condition, but incidence of deficiency has become more common, particularly in patients who have undergone bariatric surgeries for weight loss and patients in the ICU who have received greater than 7–10 days of CRRT (Curr Opin Crit Care 2021;27:367-77; Nutr Clin Pract 2018;33:439-46). Classic presentation of copper deficiency includes a microcytic anemia unresponsive to iron therapy, pancytopenia, neuropathies and myelopathies presenting as numbness, tingling, pain, weakness, loss of coordination, falls, vision changes, and dysphagia. Clinical signs may mimic myelodysplastic syndromes and may be masked by findings that are common among critically ill patients (Practical Gastro 2020;44:24-32). Rather than omitting copper from PN in patients with hyperbilirubinemia (a common practice historically because of concern for accumulation), this author suggests checking a serum copper level along with a c-reactive protein level with empiric provision of copper 0.3 mg daily in PN until copper level returns (typically a send-out test). Because copper levels increase in the setting of inflammation, one can be confident that a serum copper level below the normal range in the presence of an elevated C-reactive protein concentration is indicative of deficiency (Clin Nutr 2022;41:1357-424). Close monitoring of levels should continue in this case while short courses of repletion doses are provided, especially if clearance of copper is impaired (e.g. with severe hyperbilirubinemia).

iii. Chromium 10–12 mcg/day normal requirements, up to 20 mcg/day for diarrhea. Commercially available PN components have significant levels of chromium contamination. One study found that chromium was present in 65.6% of all PN components (JPEN J Parenter Enteral Nutr 2019;43:970-76). Therefore, supplementation with additional chromium in the PN formula is usually unnecessary. Deficiency is rare. Classic presentation of deficiency is hyperglycemia.

iv. Manganese 150–300 mcg/day is likely sufficient. Some studies state that the amount of manganese contamination in the compounding of PN may be adequate as opposed to supplementation. Other literature supports a dose of 55 mcg/day in PN formula to maintain stable whole blood manganese levels (Am J Clin Nutr 2002;75:112-8). Deficiency is very rare. Deficiency has been reported to present as a “diaper rash.” Several case reports of manganese toxicity associated with liver disease and high manganese intake (800 mcg – 1 mg/day) (Nutrition 2001;17:689-93). Signs and symptoms of toxicity emulate those of Parkinson disease.

v. Selenium 60 mcg/day up to 120 mcg/day for patients with diarrhea or short bowel syndrome. Deficiency results in extreme muscle weakness and congestive cardiomyopathy. Classic presentation with cardiomyopathy has been termed *Keshan disease* (named after a province in China where the first cases of selenium deficiency with cardiomyopathy were discovered).

vi. Typical trace elements requirements can be provided with 1 mL per day of trace elements injection 4 (dose per 1 mL: zinc 3 mg, copper 0.3 mg, manganese 55 mcg, selenium 60 mcg). This is the first FDA-approved multi-trace product, and it replaced MTE-5, which was phased out of production in 2020. It is important to note that this four ingredient product is not equivalent to the previously available multi-trace 4 (MTE-4) product as it contains different doses of trace elements and does not contain chromium. Its formulation is more consistent with current recommendations for parenteral trace elements requirements than previous multi-trace elements products.

        - vii. It is common clinical practice to withhold copper and manganese in the PN formulation for patients with hepatobiliary/cholestatic liver disease or a direct (conjugated) bilirubin concentration greater than 2 mg/dL. With this practice, the multitrace elements (MTE) product is omitted from the PN solution, and zinc and selenium are added separately. However, with the MTE product reformulation in 2020, which substantially reduced the dose of copper and manganese, and the growing body of literature describing micronutrient deficiencies in critically ill patients, it is unclear whether this practice is warranted for all patients with hyperbilirubinemia (refer to previous section on copper for more information).
        - viii. Some clinicians withhold selenium for patients with significant renal disease who do not receive hemodialysis or CRRT, though data in support of this practice are lacking. This can be accomplished by providing the desired trace element ingredients individually.
    - h. Shortages of PN ingredients
        - i. Numerous global and national events have resulted in critical shortages of almost every PN ingredient over the last several decades. This has led to errors and substandard practice for PN management (JPEN J Parenter Enteral Nutr 2012;36:44S-7S).
        - ii. Considerations for management of PN shortages are published by ASPEN and should be referenced during times of shortages (www.nutritioncare.org/ProductShortages/).

6. Should supplemental PN (SPN) be administered to patients intolerant of EN:
    - a. Casaer/EPaNIC study (*N Engl J Med.* 2011;365:506-517) of mostly surgical patients, randomized controlled trial: EN only for 7 days; then PN initiated (hypertonic dextrose solutions for 2 days; then PN) versus SPN in addition to whatever patients receiving EN could tolerate during the first 7 days
        - i. Worsened survival expressed as discharged alive from the ICU within 8 days (72% vs 75%), more infections (26% vs 23%), ICU length of stay greater than 3 days (51% vs 48%) with early SPN
        - ii. The patient population was limited because patients who were malnourished (BMI less than 17 kg/m^2) were excluded. In addition, about 60% of the population were cardiac surgery patients, for whom the indication for PN is questionable; 50% of patients were extubated by ICU day 2; and 70% of patients had an ICU length of stay of only 3 or 4 days (which would imply a questionable severity of critical illness). Finally, only 58% of patients in the early PN group were even administered PN (for 1 or 2 days), and only 25% patients in the late PN group ever received PN.
    - b. Heidegger (2013) (*Lancet.* 2013;381:385-393): 307 patients, 2 medical centers, randomized controlled trial: Patients who received less than 60% target from EN by day 3 with an anticipated ICU stay greater than 5 days received SPN or EN alone. SPN was discontinued by day 8.
        - i. SPN group had decreased infections (27% vs 38%).
        - ii. Smaller study than the Casaer study. Not all patients had REE measured (some were predicted REE). Protein target was only 1.2 g/kg/d. No difference in ICU/hospital length of stay, mortality
    - c. ASPEN (2022) (*JPEN J Parenter Enteral Nutr.* 2022;46:12-41). For adult critically ill patients receiving EN, it is recommended that SPN not be initiated before day 7 of ICU admission. This is a departure from the 2016 guidelines, which suggested initiation of SPN after 7 to 10 days if patients were unable to meet at least 60% of energy and energy requirements (*JPEN J Parenter Enteral Nutr.* 2016;40:159-211). Of note, the studies evaluated in the 2022 guidelines did not include patients with malnutrition.
    - d. Gao (2022) (*JAMA Surg.* 2022;157:384-393): Randomized controlled trial of 229 patients categorized as high nutrition risk (according to NRS-2002) with poor tolerance to EN after major abdominal surgery. Early SPN (day 3; E-SPN) was compared with late SPN (day 8; L-SPN). Increased energy delivery and fewer nosocomial infections were observed in patients in the E-SPN group with no differences in other complications. Application to clinical practice may be limited by the homogeneity of study patients (primarily male, Chinese), who were relatively healthy (most

patients had no comorbidities and barely met the criteria for high nutrition risk with an NRS-2002 score of 3 for most patients).

e. ESPEN ICU guidelines (2023) (*Clin Nutr*. 2023;42:1671-1689): The safety and benefits of PN should be weighed on a case-by-case basis for patients who do not tolerate EN at goal. When EN is not feasible for patients at high nutrition risk or those who are severely malnourished, initiation of low-dose PN should be carefully considered and balanced against the risks of overfeeding and refeeding.

f. Summary: When to initiate SPN in a critically ill patient remains controversial. The 2016 SCCM/ASPEN guidelines recommend that SPN be considered in all patients unable to receive at least 60% of target EN by 7–10 days, and the 2022 ASPEN guidelines recommend against SPN initiation prior to day 7 of ICU admission. However, supporting evidence has notable limitations. Many of the patients in the Casaer study should not have been given PN in the first place as it was not indicated. The majority of those patients were discontinued from ventilator support within 2 or 3 days, able to eat, and discharged from the ICU within 4 to 5 days. This study is a reminder that PN should not be given indiscriminately to patients as supported by the VA Cooperative Trial (1991) because PN resulted in increased infectious complications in perioperative GI cancer patients who were not malnourished as opposed to improved morbidity when given to those who were malnourished. The Heidegger data showed a benefit from supplemental PN in a sicker patient population than Casaer et al.'s population. Short-term supplemental PN may be indicated for patients who are anticipated to have prolonged duration of inability to use GI tract, anticipated prolonged duration of ICU stay, and who are either malnourished or who have a high level of catabolism. An evaluation of selected studies that support and question the use of supplemental PN was recently published (Nutr Clin Pract 2018;33:359-69).

Patient Cases

10. A 40-kg woman admitted to the trauma ICU receives a PN solution containing 350 g of dextrose, 160 g of amino acids, and 60 g of lipid daily. She has normal renal and hepatic function. Her most recent ABG from the morning shows a pH of 7.30, P_{CO_2} 55 mm Hg, P_{O_2} 96 mm Hg, and HCO_3 31 mEq/L. Her fingerstick BG values from the past 24 hours are 180–200 mg/dL. Which would be best to recommend regarding her PN?
    A. Decrease dextrose to 175 g/day, and increase lipid to 120 g/day.
    B. Add 20 units of regular human insulin per day to the PN solution.
    C. Decrease all the macronutrients by about one-half.
    D. Increase the acetate content of the PN solution.

Questions 11–12 pertain to the following case.
A 60-year-old man (weight 65 kg; about 90% IBW) is admitted for acute pancreatitis. After 4 days, he still has significant abdominal pain and distension without resolution. He has a fever, and blood/urine cultures are obtained. A CT scan of the abdomen reveals an ileus and an intra-abdominal abscess. He is given a goal PN regimen containing 300 g of dextrose, 70 g of amino acids, and 40 g of 20% lipids daily.

11. Which best depicts the kilocalories and protein this regimen will provide?
    A. 26 kcal/kg/day and 1.1 g/kg/day
    B. 26 kcal/kg/day and 1.5 g/kg/day
    C. 28 kcal/kg/day and 1.5 g/kg/day
    D. 30 kcal/kg/day and 1.5 g/kg/day

12. Which changes would be best for this patient's PN regimen?
    A. Increase dextrose to 400 g/day.
    B. Decrease dextrose to 200 g/day.
    C. Increase protein to 100 g/day.
    D. Increase lipids to 70 g/day.

E. Timing of Initiation of Nutrition Support: Early or not for ICU patients:
    1. SCCM/ASPEN (2016) (*JPEN J Parenter Enteral Nutr.* 2016;40:159-211): Early EN should be initiated within 24 to 48 hours in the critically ill patient who is unable to maintain volitional intake once the patient is hemodynamically stable. It is suggested that very early EN (within 4-6 hours, if possible) be initiated in a patient with burn injury.
    2. Surviving Sepsis Campaign guidelines (2016) (*Crit Care Med.* 2017;45:486-552): EN should be initiated early rather than a complete fast or only intravenous glucose in critically ill patients with sepsis or septic shock who can be fed enterally.
    3. ESPEN ICU guidelines (2023) (*Clin Nutr.* 2023;42:1671-1689): If oral intake is not possible and there are no contraindications to EN, EN should be initiated within 48 hours rather than delaying EN or initiating PN.
    4. Summary: The data are confusing because several studies have used different times for the definition of early nutrition therapy: 24, 36, 48, and 72 hours. Most evidence-based clinicians would suggest that EN therapy be initiated for most patients within 48 hours of ICU admission and no later than 72 hours. Surgical ICU patients, including those with trauma and thermal injury, have been more consistently shown to benefit from early EN than medical ICU patients, for whom results are more variable.

5. Summary: The data are confusing because several studies have used different times for the definition of early nutrition therapy: 24, 36, 48, and 72 hours. Most evidence-based clinicians would suggest that enteral nutrition therapy be initiated for most patients within 48 hours of ICU admission and no later than 72 hours. Surgical ICU patients, including those with trauma and thermal injury, have been more consistently shown to benefit from early EN as opposed to medical ICU patients, for whom results are more variable.

F. Glycemic Control

1. Definition of the appropriate BG target range
   a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): A BG of 150 mg/dL or greater should trigger initiation of insulin therapy to keep BG less than 150 mg/dL for most patients and maintain BG absolutely less than 180 mg/dL.
   b. ASPEN guidelines (2013) (JPEN J Parenter Enteral Nutr 2013;37:23-36): A target BG range of 140–180 mg/dL is recommended.
   c. Surviving Sepsis Campaign guidelines (2016) (Crit Care Med 2017;45:486-552): An insulin dosing protocol to keep BG less than 180 mg/dL, rather than an upper target of 110 mg/dL, is recommended when the patient has two consecutive BG measurements greater than 180 mg/dL.
   d. American Diabetes Association (2023) (Diabetes Care 2023;46(suppl 1):S267-78): An insulin infusion should be used to control hyperglycemia, starting with a threshold of greater than or equal to 180 mg/dL. BG should be maintained between 140 and 180 mg/dL for most critically ill patients. More stringent goals such as 110–140 mg/dL or 100–180 mg/dL may be more appropriate for selected critically ill patients, as long as this can be accomplished without significant hypoglycemia.
   e. SCCM guidelines (2024) (*Crit Care Med*. 2024;52(4):e161-e181): Clinicians should initiate protocols to manage persistent hyperglycemia, defined as BG greater than 180 mg/dL. Continuous infusions are preferred to subcutaneous insulin, especially in acute illness. The goal BG should be greater than 140 mg/dL, rather than more stringent targets of 80 to 139 mg/dL, while receiving an insulin infusion. Frequency of BG monitoring should be no less than every 1 hour while the patient is receiving intravenous insulin.
   f. Summary: Many evidence-based clinicians use a target BG range of 140–180 mg/dL when caring for patients in a mixed medical-surgical ICU. A growing amount of evidence from smaller studies shows that certain subpopulations such as trauma, traumatic brain injury, cardiothoracic surgery, and thermal injury may benefit from tighter BG (e.g., less than 140–150 mg/dL) control if it can be done safely without hypoglycemia (Crit Care Med 2012;40:3251-76; Nutr Clin Pract 2014;29:534-41).
2. BG monitoring frequency
   a. SCCM guidelines (2012) (Crit Care Med 2012;40:3251-76): BG should be monitored every 1–2 hours for most patients receiving an insulin infusion; monitoring every 4 hours is not recommended because of the risk of unrecognized hypoglycemia.
   b. Surviving Sepsis Campaign guidelines (2016) (Crit Care Med 2017;45:486-552): BG should be monitored every 1–2 hours during the insulin infusion and then extended to every 4 hours thereafter once stability in BG control is achieved.
   c. American Diabetes Association (2023) (Diabetes Care 2023;46(suppl 1):S267-78): BG should be monitored every ½–2 hours during the insulin infusion.
3. Hypoglycemia
   a. Most guidelines define hypoglycemia as a BG less than 70 mg/dL because increased glucagon, catecholamine, and growth hormone production occurs when the BG falls below this concentration. Mild to moderate hypoglycemia is usually defined as a BG concentration of 40–60 mg/dL (because autonomic symptoms often appear) and severe (life-threatening) hypoglycemia as less than 40 mg/dL.
   b. Most common risk factors for hypoglycemia during insulin therapy (*Crit Care Med* 2007;35: 2262-7; Crit Care Med 2006;34:96-101)

            i. Excessive insulin dose
            ii. Abrupt discontinuation of EN or PN without an adjustment in the insulin therapy (purported to cause 62% of severe hypoglycemic events in the 2006 Van den Berghe trial of medical ICU patients) (Crit Care Med 2012;40:3251-76)
            iii. Decreasing steroid dose while on insulin therapy
            iv. Hepatic failure
            v. Renal failure (half-life of insulin is prolonged, impaired renal gluconeogenesis in response to hypoglycemia)
            vi. Advanced age
            vii. Inotropes, vasopressor agents, octreotide with insulin therapy
            viii. Sepsis

4. Transitioning from a continuous intravenous insulin infusion
    a. Lack of a transition plan results in loss of glycemic control. Different methods have been described in the literature, and the best approach depends on whether the patient is transitioning to an oral diet, bolus EN, or continuous EN (JPEN J Parenter Enteral Nutr 2013;37:506-16; Crit Care Med 2012;40:3251-76; ASPEN Adult Nutrition Support Core Curriculum 2012:580-602).
    b. Once stable, ICU patients with type 1 or 2 diabetes receiving insulin infusions at greater than 0.5 unit/hour or those with stress-induced hyperglycemia receiving at rates greater than 1 unit/hour should be transitioned from an intravenous insulin infusion to a basal-bolus insulin regimen before the insulin infusion is discontinued. Several criteria should be met before transitioning to a basal-bolus regimen, including no foreseeable interruptions to nutrition for procedures, resolution of any peripheral edema, and discontinuation of all vasopressors (Crit Care Med 2012;40:3251-76).
    c. Transitioning from a continuous intravenous regular insulin infusion to a subcutaneous basal-bolus regimen: A long-acting insulin such as glargine administered every 24 hours can be used for basal coverage with initial dosing at 60%–80% of the total daily dose required from the insulin infusion. The first dose should be administered 2–4 hours before discontinuing the insulin infusion (Crit Care Med 2012;40:3251-76). Factors affecting serum blood glucose and patient response to insulin therapy should be incorporated into clinical decisions related to insulin dosing. Bolus insulin regimens are designed with rapid-acting, short-acting, or regular insulin doses to be provided as scheduled doses before meals and/or correction doses based on BG measurements (i.e., every 4–6 hours); correction doses based on BG measurements may be more appropriate for patients receiving continuous forms of nutrition support such as EN or PN. A protocol for using intermediate-acting insulin (NPH [neutral protamine Hagedorn]) has also been described for basal insulin coverage in patients receiving continuous enteral nutrition (JPEN J Parenter Enteral Nutr 2013;37:506-16).

Patient Case

13. A 55-year-old woman (weight 75 kg) without diabetes is given PN after a major GI resection. She has been weaned from mechanical ventilation and is being transferred from the ICU to the floor. Her current PN formulation is 200 g of dextrose (1.8 mg/kg/minute), 110 g of amino acids, and 80 g of lipids (1.1 g/kg/day), which meets her goal requirements at 26 kcal/kg/day and 1.5 g/kg/day of protein. It contains regular human insulin at 20 units/day. During the past 24 hours, her fingerstick BG measurements have been 170–210 mg/dL, and her serum glucose concentration is 182 mg/dL. She has received 14 units of sliding-scale regular human insulin coverage. Which would be best to suggest for optimal glycemic control?

    A. Increase regular insulin to 30 units/day.
    B. Decrease dextrose to 100 g/day.
    C. Increase regular insulin to 50 units/day.
    D. Do not change the current regimen.

G. Nutrition considerations with coronavirus disease 2019 (COVID-19)
    1. Several guidance documents have been released with specific recommendations for nutrition for patients with COVID-19 admitted to the ICU (https://www.nutritioncare.org/COVID19/). General recommendations from critical care nutrition guidelines (JPEN J Parenter Enteral Nutr 2016;40:159-211; Clin Nutr 2023;42:1671-89) are still applicable with an emphasis on preserving resources, clustering of care, and modifying clinical practices for prevention of transmission. Of note, these guidelines are primarily based on expert opinion, and many recommendations were made with the consideration of minimizing the risk to hospital staff. Publication of these recommendations also predates vaccine availability, and the guidelines may represent a risk-benefit perspective that warrants reconsideration as further knowledge is gained about the care of critically ill patients with COVID-19.
    2. Evidence suggests that patients with COVID-19 who are at higher nutrition risk have poorer outcomes (JPEN J Parenter Enteral Nutr 2021; 45:32-42.). Therefore, close monitoring of their nutritional adequacy is essential.
    3. Enteral nutrition
        a. Bedside enteral tube placement is preferred, and some guidance documents recommend that complicated feeding tube placements (involving radiology or endoscopy) should be avoided.
        b. Continuous EN is preferred over bolus EN regimens.
        c. Supplements to EN (i.e., protein or fiber) should be scheduled once daily instead of more frequent dosing.
        d. Weight-based estimations for requirements are preferred to minimize healthcare workers' exposure for indirect calorimetry. However, ongoing research suggests a persistence of hypermetabolism for up to 3 weeks after intubation in some patients with COVID-19, in which case weight-based equations may significantly underestimate energy needs (Crit Care 2020;24:581).
        e. Prone positioning is not a contraindication to EN. Early EN practices should continue in this setting, with initiation at trophic doses and advancement as tolerated. The head of the bed should be elevated to at least 10 to 25 degrees.
    4. Parenteral nutrition
        a. PN should be considered earlier if practical or clinical barriers to EN are present and prevent adequate nutrition delivery.
        b. Gastrointestinal involvement of COVID-19 may result in intolerance to EN and warrant initiation of PN.
        c. PN formulas should be formulated with the minimum volume, especially in the presence of Acute Respiratory Distress Syndrome or volume overload.
        d. Careful monitoring of serum triglycerides is warranted with provision of ILE due to reports of severe hypertriglyceridemia in patients with COVID-19.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

Hyperglycemia and other causes of non-hypotonic hyponatremia have been excluded. Urine osmolality is greater than 100 mOsm/kg, which rules out psychogenic polydipsia, and a large amount of hypotonic fluids were not being given. Urine sodium was greater than 30 mEq/L, and the patient did not receive diuretic therapy or have kidney disease. The patient appeared to be normovolemic without evidence of significant edema (expansion of the ECF compartment). Because the patient also has pneumonia (a common cause of SIADH), all of these factors indicate that the patient has hyponatremia caused by SIADH (Answer D is correct). Answer A is incorrect because the serum glucose concentration is not high enough to cause hyponatremia; nor has the patient received mannitol, glycine: nor is the patient hypertriglyceridemic. Answer B is unlikely because there was no evidence of adrenal insufficiency given in the case. Answer C is impossible because the patient did not have a traumatic brain injury.

2. **Answer: B**

Fluid restriction is the most appropriate treatment of SIADH (Answer B is correct). The “vaptans” may also be considered; however, this was not a choice. Answer A is incorrect because giving salt tabs may result in worsened fluid overload and edema. Answer C is incorrect for the same reason as Answer A. Answer D is incorrect because the severity of hyponatremia and lack of symptoms does not warrant the emergency use of hypertonic saline.

3. **Answer: D**

The best way to fluid-restrict an enterally fed patient is to use the most concentrated formulas, which are the 2-kcal/mL formulations that are specifically designed for patients with congestive heart failure. Unfortunately, protein intake may be inadequate with the use of these formulations in certain populations, and supplemental protein may have to be provided. Answers A, B, and C are incorrect because they do not result in the appropriate therapeutic decision to reduce fluid intake.

4. **Answer: B**

These dosages should be selected as the correct answer because they follow the dosing guidelines given in this chapter (unlike the doses given in answers A, C, D). Given that the patient is NPO with intolerance to anything by mouth, oral options (Answers A and D) are not practical. If the patient had a history of significant recent weight loss or if he did not respond adequately to these doses, the dose could be increased. Answer C is not correct as the dosage of phosphorus is excessive. Supplemental potassium and phosphorus would be added to the PN solution, in addition to daily intravenous doses of potassium and phosphorus.

5. **Answer: B**

Because it takes about 48 hours for serum magnesium to redistribute, the next day’s serum magnesium concentration is falsely elevated. In general, it will take 4–5 days to replete this patient’s magnesium deficiency (presumably caused by chronic alcohol ingestion). Thus, answer B would be the best option for this patient. Given that the patient is NPO, oral dosing options (answer A) are less desirable. Answer C is incorrect because it is too aggressive a dosage given the current serum magnesium concentration of 2.0 mg/dL (despite it being falsely elevated). Supplemental magnesium would be added to the PN solution in addition to daily doses of intravenous magnesium sulfate if he remained low or in the low-normal range or if he was also hypocalcemic (because hypomagnesemia can elicit hypocalcemia secondary to end-organ resistance to parathyroid hormone). Answer D is incorrect as the serum magnesium concentration is falsely elevated to within the normal range but has not fully redistributed yet. It would be anticipated that the concentration will decrease the following day since it takes multiple days to replenish magnesium stores.

6. **Answer: C**

Although critical illness (Answer D) and fluid resuscitation therapy may have been a factor in the development of his hypocalcemia, massive blood transfusion is the most profound cause. Citrate, added to the blood as an anticoagulant, readily binds calcium and can cause hypocalcemia. Previous studies have shown that hypocalcemia is common when patients are given more than 5 units of blood at a time (Answer C is correct). Answer A is incorrect because a low-normal serum magnesium concentration of 1.8 mg/dL is unlikely to contribute to the pathogenesis of hypocalcemia. A serum magnesium concentration of less than or equal to 1.5 mg/dL is more likely to contribute to the pathogenesis of hypocalcemia. Answer B is incorrect because a urine output of 0.5 mL/kg/hr is not excessive.

7. **Answer: B**

A short-term intravenous infusion of 4 g of calcium gluconate (1 g = 4.6 mEq) for 4 hours has been shown to be a safe and effective therapeutic regimen for moderate to severe hypocalcemia (ionized calcium less than 1 mmol/L) (Answer B is correct). Answer A is incorrect because it is an insufficient dosage of elemental calcium. A bolus/push dose of calcium chloride (1 g = 13.6 mEq), as given in answer C, would be an effective means for treating symptomatic severe hyperkalemia, but it would be unnecessarily aggressive for treating hypocalcemia in this patient scenario. Answer D is incorrect because the moderate to severe hypocalcemia should be corrected in this post-operative trauma patient who is anemic and at high risk for bleeding complications.

8. **Answer: A**

Examination of the pH indicates that the patient has an acidemia because it is lower than 7.35. Looking at P_{CO_2} and serum bicarbonate would indicate that the primary etiology is metabolic because both are low. Calculation of the AG (145 − 118 − 18 =9) shows that no AG is present (Answers B and C are incorrect). A correction for serum albumin concentration is not needed because it is normal. The serum lactate is near the high end of the normal range but still within the normal range. This would indicate that the patient's dehydration has not become so extreme that a significant decrease in tissue perfusion was not evident (yet). Respiratory compensation appears to be intact ([1.5 x 17] + 8 = 33 vs. 34 mm Hg) on the blood gas, and it appears that the patient's history of smoking did not compromise her ability to mount a reasonable respiratory response to the acidosis. The serum chloride of 118 mEq/L indicates hyperchloremia. A non-AG hyperchloremic metabolic acidosis is common for patients with severe diarrhea. The low serum potassium and magnesium would also strongly suggest that the patient has significant diarrhea (Answer A is correct). Answer D is incorrect because the decreased P_{CO_2} is in response to the metabolic acidosis and the patient does not have a metabolic alkalosis but rather an acidosis.

9. **Answer: C**

Initial therapy with lactated Ringer solution would be the ideal choice (Answer C is correct). Treatment with 0.9% sodium chloride (Answer B) is incorrect because it would worsen the hyperchloremic acidosis. A 5% dextrose solution (Answer D) would be a poor choice because sodium/isotonic fluids are necessary to restore intravascular volume. Because the severity of the patient's acidemia is mild (pH 7.29), aggressive therapy with sodium bicarbonate is not indicated. After the first day of lactated Ringer solution to restore intravascular volume and improve pH, it would be reasonable to change to 0.45% sodium chloride to continue to restore volume depletion, depending on the patient's response to the lactated Ringer solution (e.g., restoration of normal pH, adequate urine output, resolution of tachycardia). Thus, answer A would be incorrect as the question asked for the most appropriate *initial* treatment. Of course, aggressive potassium and magnesium repletion is indicated as well. This could be done with infusions as previously discussed, and it would be reasonable to add 20 mEq of potassium chloride per liter to the 0.45% sodium chloride upon discontinuation of the lactated Ringer solution.

10. **Answer: C**

The current PN regimen provides 61 kcal/kg/day total (glucose 6.1 mg/kg/minute and lipid emulsion 1.5 g/kg/day) and protein 4 g/kg/day. The PN regimen represents gross overfeeding of this small woman and can explain her hyperglycemia and hypercapnia. Cutting all macronutrients by about one-half would result in a more reasonable regimen for this patient: 30 kcal/kg/day (glucose 3 mg/kg/minute and lipid emulsion 0.8 g/kg/day) and protein 2 g/kg/day. Because she is so small (weight 40 kg), it would be important to double-check the weight-based calculation to see whether this new regimen is appropriate to meet her caloric needs without overfeeding by calculating the BEE using the Harris-Benedict equation for women (caloric intake should not exceed 1.3–1.5 x BEE for a critically ill patient with traumatic injuries) (Answer C is correct). Although answer A reduces the respiratory quotient of the nutrient admixture, this will not solve the primary problem of overfeeding the patient because excessive calories are being provided. Answers B and D may help with the consequences of overfeeding (e.g., hyperglycemia and respiratory acidosis) but do not address the primary problem (overfeeding) and are inappropriate management techniques.

11. **Answer: A**
Total kilocalories per day = (300 g x 3.4 kcal/g of dextrose) + (70 g x 4 kcal/g of protein) + (40 x 10 kcal/g of lipid emulsion) = 1020 glucose kcal + 280 protein kcal + 400 lipid kcal = 1700 total kcal/65 kg = 26 kcal/kg/day. Only 20% and 30% lipid emulsions are available for PN compounding. Each solution provides 10 kcal/g of intravenous lipid (unlike 9 kcal/g with oral fat) because glycerol and phospholipids are added to the emulsion. Protein intake is 70 g/65 kg = 1.1 g/kg/day (Answer A is correct). Answers B, C, and D do not represent the correct calculations as described previously.

12. **Answer: C**
This patient is moderately stressed with a normal BMI. Appropriate energy intake would be 25–30 kcal/kg/day (1625–1950 kcal/day), and protein intake would be 1.2–2 g/kg/day (78–130 g). Increasing dextrose to 400 g/day would provide a total energy of 31 kcal/kg/day. Although this glucose intake of 4.3 mg/kg/minute does not exceed 5 mg/kg/minute, the total kcal/day from all macronutrients would exceed the recommended initial range for this patient (Answer A is incorrect). Decreasing the dextrose dose to 200 g/day would provide a total energy of 21 kcal/kg/day from all macronutrients, which is below the target energy range for this patient (Answer B is incorrect). Increasing the lipid dose to 70 g/day would provide a total energy of 31 kcal/kg/day from all macronutrients, which is above the target of 25–30 kcal/kg/day (Answer D is incorrect). A protein dose of 100 g/day would provide 1.5 g/kg/day of protein. This dose is appropriate and falls within the recommended 1.2–2 g/kg/day. Increasing the protein dose to 100 g/day while maintaining dextrose at 300 g and lipid at 40 g would provide the patient with 1820 kcal or 28 kcal/kg/day. This is an appropriate protein and energy intake for this patient (Answer C is correct).

13. **Answer: A**
Because the target BG should be within 140–180 mg/dL for this surgical patient being transferred to the floor, a modest improvement in glycemic control is indicated. Thus, answer D (no change) would be incorrect. Ideally, obligatory glucose requirements should be met (e.g., about 130 g/day plus about 80–150 g/day for wound healing) to prevent the use of amino acids for gluconeogenesis. Thus, decreasing the glucose intake to 100 g/day as described in answer B is not desirable, given the mild increases in BG concentration. The easiest method to achieve glycemic control and meet caloric needs is to modestly increase the regular human insulin content in the PN solution. Because 14 units of sliding scale insulin still appears insufficient, a modest increase in insulin appears prudent. The patient is unlikely to experience hypoglycemia with the provision of insulin at 30 units/day when given 200 g of intravenous dextrose concurrently (Answer A is correct). As the stress resolves and glycemic control improves, insulin can be decreased or eliminated from the PN solution. Answer C is incorrect because it would likely provide too much insulin, based on sliding scale coverage and current BG range, and increase the patient's risk for hypoglycemia.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

An ileus, usually detected on radiologic examination of the lower abdomen, indicates lack of motility and presence of distention and air within the small bowel. This is usually depicted as "dilated loops of bowel." Patients cannot be fed safely or efficaciously by the enteral route during an ileus (Answer C is correct). Answer A is incorrect because a feeding tube can be placed for enteral feeding of the patient with anorexia, and PN is not indicated. Answer B is incorrect because presence or absence of bowel sounds is not an accurate marker for assessing bowel function. Answer D is incorrect because a high gastric residual volume during enteral feeding, combined with abdominal distension, bloating, emesis, or regurgitation, can often be efficaciously treated with prokinetic pharmacotherapy or advancement of the feeding tube into the small bowel with resumption of enteral feeding. In addition, the guidelines recommend against discontinuing EN for a GRV less than 500 mL in the absence of other signs of intolerance.

2. **Answer: B**

Answer B, 0.45% sodium chloride and potassium chloride 20 mEq/L, is correct given the average electrolyte composition of gastric fluid (see Table 4 regarding the electrolyte composition of GI fluids). Answers A, C, and D are incorrect because they do not as accurately replace the electrolyte content that is lost from gastric fluid output.

3. **Answer: A**

With significant diarrhea, intravenous zinc requirements from GI fluid losses during critical illness increase from the normal requirements of 3–5 mg/day. Data analyses show that most patients with increased intestinal losses can achieve a positive zinc balance on 13 mg of intravenous zinc daily (Gastroenterology 1979;76:458-67). As a result, most clinicians provide additional zinc supplementation for patients with short bowel syndrome, intestinal fistulas, or prolonged and sustained diarrhea (Answer A is correct). Answer B is incorrect because copper is an extremely rare and unlikely deficiency to occur during parenteral nutrition therapy. Answers C and D are incorrect because intractable diarrhea losses are less likely to cause a deficiency, albeit with the exception of copper (especially with extreme intestinal bypass procedures for obesity).

4. **Answer: C**

Given the severity of the patient's condition (recent seizure from severe hyponatremia) and likely diagnosis of SIADH, the immediate goal should be to achieve a serum sodium concentration of greater than 120 mEq/L by short-term infusion of 3% sodium chloride (Answer C is correct). Conivaptan (Answer D) could then be given to correct the hyponatremia, limiting the increase in serum sodium concentration to less than 10–12 mEq/L/day. Fluid restriction is imperative and is the primary overall management technique for this patient. Answer A is incorrect because a more rapid response is imperative because of the patient's seizure and severity of the condition. Answer B is incorrect because it would be a potentially life-threatening error by providing more ADH-like substance and because it is used to treat diabetes insipidus (the opposite condition of SIADH).

5. **Answer: B**

Studies show that increases in mesenteric potassium concentrations detected by potassium sensors in the splanchnic vascular bed evoke increased renal potassium excretion (feed-forward regulation of potassium homeostasis), even before regulation by aldosterone (classic feedback regulation) (Answer B is correct). The bioavailability of enteral potassium is 95%–100% in the absence of aberrations in GI motility, function, or anatomy. A primary difference between enteral and parenteral potassium is that the rate of absorption is slower with enteral potassium (Answer A is incorrect). Intravenous potassium administration can inadvertently be infused too quickly (it is acceptable to infuse potassium at 10 mEq/hour for patients without a cardiac monitor and up to 20 mEq/hour for those with a monitor). Answer C is incorrect because potassium chloride elixir or solution is an effective means for providing potassium when given intra-gastrically. It generally only causes diarrhea when given in higher doses or when administered directly into the small bowel through a feeding jejunostomy because it is a hypertonic solution. Answer D is a nonsensible answer.

6. **Answer: D**

Answer D, *additional magnesium therapy should be given daily for the next 4–5 days,* is correct because it takes 48 hours for magnesium to equilibrate after a short-term infusion, making Answer A incorrect. Although Answer B is common in clinical practice, failure to provide additional magnesium repletion in the setting of a normal serum magnesium concentration the day after a large intravenous dosage usually causes serum concentrations to decrease below the normal range again over the next 1–2 days as magnesium equilibrates. Thus, Answer B is not ideal management and is incorrect. Answer C is incorrect because hypocalcemia should autocorrect with magnesium supplementation within 48 hours of magnesium therapy; however, calcium therapy can be given concurrently, if necessary (symptomatic or ionized calcium concentration less than 1 mmol/L).

7. **Answer: D**

The current PN formula prescribed provides 3240 kcal/day (42 kcal/kg/day with a glucose infusion rate of 5.8 mg/kg/minute), which is an excessive amount of energy for this patient, and he has possible signs of overfeeding in the form of hyperglycemia. Answer D is correct because decreasing the dextrose dose to 315 g would appropriately bring the patient's energy down to 2101 kcal/day (27 kcal/kg/day with a glucose infusion rate of 2.8 mg/kg/minute). An initial energy goal of 25–30 kcal/kg/day is appropriate for this patient, and by significantly decreasing the dextrose and total energy load provided in the PN, his hyperglycemia should improve. Answer A is incorrect because the additional insulin will not address the issue of overfeeding, and sliding-scale insulin is unlikely to provide adequate glycemic control for this patient. Answer B is incorrect because temporarily adjusting the dextrose dose will not correct the issue of overfeeding in the long term. Answer C is incorrect because the total energy provided with these changes would still provide 37 kcal/kg/day and exceed the appropriate initial goal of 25–30 kcal/kg/day.

8. **Answer: B**

This patient's pH is high at 7.46 mmHg so his primary disorder is an alkalosis (Answer D is incorrect). His serum HCO_3 is 20 mEq/L (low) and P_{CO_2} is 31 mmHg (low). His high pH and low P_{CO_2} indicate that his primary disorder is a respiratory alkalosis (Answer C is incorrect). However, his laboratory values reveal an AG of 19 (141 − 102 − 20 = 19), which indicates that a metabolic acidosis is present, regardless of his pH or HCO_3 values (Answer A is incorrect). His delta ratio is 1.25 ([19−14] / [24−20]), which indicates that an AG metabolic acidosis is present with no other hidden metabolic process. Answer B is correct.

PROTOCOL DEVELOPMENT AND QUALITY IMPROVEMENT

JAIME ROBENOLT GRAY, PHARM.D., FCCM, BCCCP

TEMPLE UNIVERSITY HEALTH SYSTEM
DEPARTMENT OF PHARMACY
PHILADELPHIA, PENNSYLVANIA

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JAIME ROBENOLT GRAY, PHARM.D., FCCM, BCCCP

TEMPLE UNIVERSITY HEALTH SYSTEM
DEPARTMENT OF PHARMACY
PHILADELPHIA, PENNSYLVANIA

Learning Objectives

1. Determine the steps involved in the development of a guideline and/or policy.
2. Design a medication use evaluation (MUE) with selection of an appropriate medication and/or medication-related process suitable for an MUE.
3. Determine the appropriate quality improvement tool to use in order to optimize outcomes in a critically ill patient population.
4. Identify processes or quality improvement initiatives that would benefit from a gap analysis.
5. Describe the types of pharmacotherapeutic interventions and documentation processes to justify the value of clinical pharmacy services.

Abbreviations in This Chapter

ADE	Adverse drug event
ASHP	American Society of Health-System Pharmacists
CMS	Centers for Medicare & Medicaid Services
CPOE	Computerized provider order entry
CPS	Clinical pharmacy services
DUE	Drug use evaluation
EBM	Evidence-based medicine
EHR	Electronic health record
ICU	Intensive care unit
LOS	Length of stay
MUE	Medication use evaluation
PAI	Practice Advancement Initiative
PI	Performance improvement
P&T	Pharmacy and therapeutics (committee)
QA	Quality assurance
QI	Quality improvement
SUP	Stress ulcer prophylaxis
TJC	The Joint Commission

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. As the clinical coordinator/manager, you have received a request to add the critical care pharmacist's review of all intensive care unit (ICU) patients. You recognize that you lack the necessary personnel to accomplish this request. Which justification method would offer the most significant financial impact on the institution to justify the position?
   A. Developing protocols in the critically ill patient.
   B. Reducing prescribing errors.
   C. Reducing medication administration errors.
   D. Implementation of an anticoagulation reversal stewardship program.

2. You are the critical care pharmacist implementing a delirium screening tool in critically ill patients according to the Society of Critical Care Medicine guidelines. Which would best be described as a practice environment barrier to implementing delirium screening in your ICU?
   A. The nursing standard work does not include delirium screening.
   B. Screening process takes up valuable nursing time.
   C. Providers are unfamiliar with how to perform delirium screening.
   D. Providers believe their knowledge of bedside delirium is adequate and does not require a screening tool.

3. The pharmacy and therapeutics (P&T) committee would like to assess the use of pharmacotherapy in stress ulcer prophylaxis (SUP) in the ICU. Which is the best method for making this evaluation?
   A. Perform a medication use evaluation (MUE).
   B. Administer a performance improvement (PI) initiative.
   C. Review adverse drug event (ADE) data from the ICU.
   D. Review medication error data from the ICU.

4. Which medication use process is best suited for an MUE?
   A. Pharmacist verification times for routine orders in the ICU.
   B. Management of warfarin-induced hypoprothrombinemia.
   C. Drug interaction warnings on the computerized provider order entry (CPOE) system.
   D. Duplicate warnings on the CPOE system.

5. You have been asked to develop a quality improvement (QI) strategy for your ICU regarding when to institute targeted temperature management in patients after cardiac arrest. The current process has been defined, and best practices for targeted temperature management have been outlined. You identify key stakeholders in this patient population to collaborate with you in this process improvement. Which is the next best step in developing the QI program?
   A. Determine which patients with cardiac arrest should receive targeted temperature management.
   B. Evaluate the current clinical guidelines associated with targeted temperature management.
   C. Determine the current process of targeted temperature management.
   D. Evaluate the data associated with patients receiving targeted temperature management.

6. You obtain data related to time to administration of immediate antibiotics for sepsis from your CPOE system in order to determine a baseline metric for quality improvement. Using the define, measure, analyze, improve, control (DMAIC) method, which step describes the process phase to determine the baseline time to antibiotics?
   A. Data are collected.
   B. Methods are established.
   C. Change process is implemented.
   D. Data are analyzed.

7. Which metric best quantifies a critical care pharmacist's activities?
   A. Weighing each variable to quantify measured activities.
   B. Number of cardiac arrest codes attended each month.
   C. Number and severity of hospital-acquired *Clostridioides difficile* infections each year.
   D. Number of in-services provided each year.

8. As the clinical pharmacist in the ICU, you are asked to evaluate the quality initiatives specific to critically ill patients. Which best describes a Centers for Medicare & Medicaid Services (CMS) quality metric?
   A. Sepsis management bundle and venous thromboembolism prophylaxis.
   B. Thrombolytic therapy for stroke and SUP.
   C. Heart failure readmission and pneumonia vaccination rates.
   D. Ventilator bundles and acute coronary syndrome readmission rates.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 3: Professional Practice
    a. Quality of Care
        i. 3A2, 3A3, 3A4, 3A7
    b. Practice Management
        i. 3B1

I. POLICY AND GUIDELINE DEVELOPMENT

Objective: Critical care pharmacists should participate in developing ICU and institutional policies, procedures, guidelines, and education.

- A. Policy and Procedure
  - 1. Policy – A course or plan of action; written policies establish standards of practice or quality/compliance measures and protects against error. Policies intend to show the "why" behind an action and include a description of "what," "when," "who," or "where" actions should occur in a specific situation. Most policies are mandatory and may result in disciplinary action if not followed. Policy is based on well-defined standards including those that may be required to comply with laws, regulations, or contracts.
    - a. Benefits
      - i. Improves consistency and efficiency of work processes
      - ii. Provides a training tool during a new employee's orientation
      - iii. Provides reference material for education and practice
      - iv. Minimizes practice variations
      - v. Reduces the organizational risk by mandating compliance
    - b. Development and implementation should involve all relevant team members to ensure all concerns are addressed and to promote input from all stakeholders.
    - c. Examples of policies:
      - i. Acute pulmonary embolism response team
      - ii. High-alert medication list and safety standards
      - iii. Pharmacist initiated automatic therapeutic interchange
      - iv. Pharmacist-initiated intravenous to oral conversion
  - 2. Procedure – A series of actions or tasks performed in a specific way or sequence that is intended to achieve a desired result or accomplish a task in a consistent manner; the "how" to achieve the desired outcome or comply with a stated policy.
    - a. Requires approval by the organizational committee
    - b. Describes each team member's responsibility
    - c. Defines the expected outcome(s)
    - d. Procedures may be described in the following forms:
      - i. Written instructions
      - ii. Flowcharts
      - iii. Checklists
    - e. Can be used as a QI tool or a source of measures
    - f. Examples of procedures:
      - i. Central line placement
      - ii. Medication event reporting
      - iii. Use of the AddEase Administration System
      - iv. Downtime procedures during system outages or natural disasters

- B. Clinical Guidelines/Protocol – Evidence-based statements that assist practitioners with decisions for specific clinical circumstances. Should include all aspects of care including the following: Patients that are excluded from the treatment or have contraindications, initiation criteria, dosing (if applicable), titration, monitoring, education, duration of therapy, etc.
  - 1. Supports clinical decision-making by defining best practice
  - 2. Uses evidence-based and standardized treatment options
  - 3. Developed by examining the evidence and gaining consensus among practitioners

4. Interdisciplinary team effort: Patient, physician/prescriber, nurse, respiratory therapist, pharmacist, clinical dietitian, physical therapist, social worker and/or case manager, hospital administrators, and patient's family/support network
5. Voluntary – Allows for deviation depending on clinical scenario
6. Protocol can be an extension of a clinical policy or procedure.
7. Clinical guidelines and protocols are often kept separate from institutional policies and procedures.
8. Examples of disease management guidelines include:
    a. Pulmonary embolism therapeutic management
    b. Pain, Agitation, Delirium, Immobility, and Sleep (PADIS) management
    c. Spontaneous awakening and breathing trials
    d. Anticoagulation reversal
9. Critical care pathways
10. Formulary proposals
11. Medication reconciliation for admission and transfer within the health care system
12. Clinical decision support
    a. Consider ways to incorporate guidelines/protocols into CPOE to facilitate ordering and monitoring in conjunction with the guideline/protocol.

C. Framework of a Policy and/or Procedure

Critical care pharmacists should lead, or be actively involved with, the assessment of medication-related guidelines, protocols, practice changes, or PI initiatives in the ICU.

1. Purpose – For whom the policy is intended, why the policy is needed, and the desired goals
2. Definitions – Provide the reader with a clear understanding of the language
3. Intent of the policy
4. Provisions
5. Procedure
6. Resources/references
7. Owner
8. Date created/modified/last reviewed
9. Approvals

D. How to Develop Policies

1. Planning
    a. Define and prioritize policy goals and objectives.
    b. Identify key stakeholders and include them in the policy development process.
    c. Appoint a project facilitator/leader.
    d. Clearly delineate each team member's roles and responsibilities in the policy development process.
    e. Develop a strategy for tracking and managing each group's progress.
2. Consultative process for developing a particular policy
    a. Solicits input from organizational or external stakeholders
    b. Promotes good relations between sites and service providers
    c. Encourages participation and feeling of ownership in the process
    d. Provides new ideas and expertise
    e. Alternative viewpoint may identify inconsistency, ambiguity, and/or duplication.
3. General steps in drafting
    a. Write a first draft.
    b. Distribute the draft, and consult across the same organization/stakeholders/experts for comments.
    c. Review feedback, both written and verbal, and amend/revise the draft.
    d. Redistribute the draft for additional/final feedback.

      e. Write the final draft.
      f. Document the date that the policy was ratified and then subsequent review dates.
      g. Committee review and approval.
      h. Incorporate the new policy into the policy and procedures.
      i. Communicate the new policy to all relevant people.
   4. Identify policy review process.
      a. Formal process may be required within the institution (i.e., standing policy and procedures committee, which develops and reviews the policy and provides recommendations and decisions).
      b. Involvement and approval from the P&T and critical care committees or other oversight committees

E. Education
   1. Create education for the key stakeholders (e.g., physicians, advanced practice providers, nurses, pharmacists, dietitian, respiratory therapists).
   2. Disseminate education through newsletters, intranet posts, in-services, huddles, quarterly updates, grand rounds, one-on-one direct education, online learning modules, etc.
   3. Assessment of education through annual competency examination, skills assessment, monthly simulation modules, etc.

F. Review of existing policies. Continuous QI requires documentation and training for pharmacists and staff. Many state boards of pharmacy are requiring reportable events to be identified and documented. Policies and procedures can also be developed for analyzing the data collected to assess causes and contributing factors so that findings can be used to improve outcomes.
   1. Every policy should regularly be reviewed for relevance and appropriateness (e.g., every 1–3 years), depending on organizational structure/standards.
   2. Monitor and evaluate compliance with, and effect on, policies and guidelines.
   3. Things to consider when reviewing a policy:
      a. Determine need for updates to the policy.
      b. Evaluation strategies
      c. Ongoing monitoring
      d. Presentation of data
      e. Consumer feedback
      f. Stakeholder feedback (e.g., physician, pharmacy, nursing, policy steering committee, critical care committee)
      g. Planning day agenda
      h. Forms: Data collection sheets, data reporting format, questionnaires
      i. Key stakeholder questionnaires
   4. Review evidence-based critical care literature and clinical practice guidelines in designing a patient-specific plan of care
      a. Definition: "The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research." (BMJ 1996;312:71)
      b. Pros and cons of evidence-based medicine (EBM)
         i. Advantages
            (a) Critical appraisal skills of the literature improve with the review of EBM.
            (b) Wasteful, outdated, or harmful practices can be abandoned.
            (c) Presupposes that we keep up-to-date; ideally, a systematic process of incorporating new EBM is included

        (d) Makes the decision-making process transparent to colleagues and patients
        (e) Leads to greater appreciation of the evidence for our practice as well as the inherent uncertainties
      ii. Disadvantages
        (a) Time-consuming
        (b) Sometimes impossible (when there is no published literature on a question)
        (c) Useful papers may be disregarded because of minor blemishes (rescue bias).
        (d) Contradictory study findings leading to differences in interpretation of benefit
        (e) No science to tell us how robust the evidence must be for it to be incorporated into clinical practice
        (f) External validity is subjective, and evidence can be misapplied.
        (g) Easy-to-prove techniques more favored in literature
        (h) It is never "up-to-date."
        (i) Tends to emphasize the priority of randomized controlled trials (which have inherent flaws) to the exclusion of other study designs (which may be appropriate in certain settings)
        (j) May underemphasize patient values and interests
        (k) Publications with favorable results are more likely to be published than are those without favorable results (publication bias).
  5. Barriers to implementing evidence
    a. Practice environment (organizational context)
      i. Financial disincentives – Lack of reimbursement
      ii. Organizational constraints – Lack of time; insufficient leadership or administrative support; staffing, equipment, or resource constraints
      iii. Perception of liability – Risk of formal complaint
      iv. The patient's expectations – Expressed wishes related to care
    b. Prevailing opinion (social context)
      i. Standard work – Usual routine
      ii. Opinion leaders – Key individuals not in agreement with evidence
      iii. Medical training – Obsolete knowledge
      iv. Advocacy – By pharmaceutical companies
    c. Knowledge, skills, and attitudes (professional context)
      i. Clinical uncertainty – Necessary test for vague symptoms
      ii. Sense of competence – Self-confidence in skills
      iii. Compulsion to act – Need to do something
      iv. Information overload – Inability to appraise evidence

G. Checklist to Follow When Developing Guidelines
  1. Scope and purpose
    a. Objectives are specifically described.
    b. Health questions covered by the guideline are specifically described.
    c. The patient population to which the guideline applies is specifically described.
  2. Stakeholder involvement
    a. Guideline development group includes individuals relevant to the guideline.
    b. Target population's views and preferences have been identified.
    c. Target users of the guideline are defined.
  3. Development of guideline
    a. Literature search is systematic.
    b. Criteria for selecting evidence are clearly defined.

    c. Strengths and limitations of evidence are described.
    d. Health benefits, adverse effects, and risks are considered when developing recommendations.
    e. Link between recommendations and supporting evidence is provided.
    f. Guideline is externally reviewed by experts.
    g. Defined times for guideline updates are provided.
  4. Clarity of recommendations
    a. Recommendations are clear and unambiguous.
    b. Different options are clearly presented.
    c. If involving medication therapy, dosing is clear, including initial starting rate and titrations for continuous infusions.
  5. Applicability
    a. Guideline describes facilitators and barriers to the application.
    b. Guideline provides tools on how it should be applied to practice.
    c. Guideline presents monitoring and/or auditing criteria.
  6. Approval
    a. Guidelines involving the use of medications should obtain appropriate committee-level approvals prior to implementation.
  7. Monitoring of adherence to the guidelines through MUEs to assess compliance or need for revisions.

H. Other considerations
  1. All policies, procedures, guidelines/protocols should be accessible during periods of electronic health system maintenance and downtime (planned and unplanned).
  2. Important to ensure each unit where these documents are used or at the institutional or health-system level are kept in a location where they can be easily accessed should a mass casualty event or downtime occur

Patient Case

1. As the critical care pharmacist, you have been asked to develop a guideline for reversal agents used in the setting of bleeding associated with anticoagulation therapy. Which is the best example of a component that should be involved in establishing the clinical pathway?
  A. Evaluate the closed-loop technology to support a clinical pathway, and establish a physician champion.
  B. Use EBM to support the clinical pathway and develop agreement among practitioners.
  C. Develop a clinical protocol, and obtain agreement among practitioners.
  D. Evaluate formulary proposals and the EBM supporting the clinical practice.

II. GAP ANALYSIS

A. A gap analysis is an assessment of a practice model that may be within your health system or pharmacy and that is compared with a best practice model (actual vs. potential performance). Within pharmacy, a gap analysis may focus on pharmacy services, pharmacy technology, or a specific medication or medication process. A gap analysis can also be used to analyze gaps in processes and between the existing outcome and the desired outcome. This process can be summarized as follows.

B. Goals of a Gap Analysis – To provide the project team with an understanding of the differences between current and best practices. An assessment must be made of the barriers that exist before best practice can be implemented successfully. A Gap Analysis should be conducted using the following steps. Using a tool to track best practices, future state, gaps, and solutions is helpful to keep all information organized and track the progress of the change to be implemented.
   1. Identify best practices and determine/define what the future state should be.
   2. Identify and review current state practices.
   3. Shadow processes or "Walk-the-Line" to experience what the current state is like.
   4. Compare ideal or future state to the current state to identify gaps.
      a. This can be categorized as fully compliant, partially compliant, in progress, noncompliant, or potentially not applicable, depending on the practice site.
   5. Evaluate potential solutions to bridge the gaps to achieve the future state.
   6. Implement change management with timeline goals for successful progress.
   7. Monitor the progress of implemented solutions to ensure the change is sustained.

C. Best Practice Evaluation
   1. Review of the primary literature
   2. Benchmarking against gold standards such as:
      a. ISMP Best Practices
      b. ISMP Safety Alert newsletters
      c. Published guidelines such as USP 797 or USP 800
      d. The Joint Commission and National Patient Safety Goals
      e. CMS Core Measures
   3. Survey practitioners – Feedback from practitioners (e.g., ICU pharmacists, nurses, physicians) may be helpful when best practices have not been published or their buy-in is essential
      a. Survey strategies
         i. Have a single well-defined objective.
         ii. Keep the survey short.
         iii. Assure respondents that survey responses will be kept anonymous (if possible).
         iv. Survey a large-enough sample to ensure meaningful results.
         v. Explain the purpose of the survey, and how you intend to use the results, in your invitation/greeting page.
         vi. Spell out the time expectations in your invitation and on the greeting page.
         vii. Survey the appropriate people.
         viii. Design the survey for easily measurable results.
         ix. Evaluate one concept per question.
         x. Avoid biasing the response.
         xi. Limit the number of required questions.
         xii. Question order matters – The first question or two should be easy and interesting.
         xiii. Create a logical flow to the questions.
         xiv. Test the survey.
         xv. Share the results and actions with the respondents.

D. A gap analysis for medication safety should include strategies for prevention and mitigation, assessment and detection, therapeutic use, critical thinking and knowledge, and education. A gap analysis should also include policies, procedures, protocols, guidelines, competencies, patient care models, educational methods, and other key components to maximize efficacy and prevent medication errors and harm.

E. Examples of a Gap Analysis Include:
   1. Centers for Disease Control and Prevention (CDC): The Core Elements of Hospital Antibiotic Stewardship Programs: Antibiotic Stewardship Program Assessment Tool (excerpt) (Appendix 1)
   2. ADE prevention related to the following medications: Opioids, anticoagulants, aminoglycosides, etc.
   3. Intravenous-to-oral conversion of antihypertensives
   4. Medication labeling
   5. Medication barcoding and scanning
   6. Narcotic diversion prevention
   7. Sterile admixture services
   8. Extemporaneous compounding services
   9. Pharmacist activities during a code or rapid response
   10. Pharmacy patient care models – Evaluating the number of ICU pharmacists to patient ratios based on workload, documentation requirements
   11. American Society of Health-System Pharmacists (ASHP) Practice Advancement Initiative (PAI) to optimize care through pharmacist-provided comprehensive medication management
   12. ICU liberation practices, including ABCDEF bundle
   13. Antibiotic streamlining
   14. Criteria-based antimicrobials and non-antimicrobials for high-cost/misused drugs
   15. Departmental professional development education
   16. Institute for Safe Medication Practices (ISMP) Targeted Medication Safety Best Practices for Hospitals
       a. Can be used to assess progress on safety recommendations from ISMP
       b. Can also be used to develop metrics related to implementation status of these best practices.
   17. The Joint Commission (TJC) Medication Management Standards

Patient Case

2. Neuromuscular blocking agents are high alert medications and have led to significant medication errors and patient harm. You noticed at your new job in the medical ICU when you went to pull rocuronium from the automated dispensing cabinet that there were no warnings on the pyxis, and it was in an open cubie pocket. You recalled ISMP having safety alerts and even a best practice regarding the safe storage and handling of neuromuscular blocking agents. Which is the best example of how to conduct a gap analysis for the safe handling and storage of neuromuscular blocking agents?
   A. Conduct a survey of other institutions to see how they are handling the storage of NMBs and compare with practice at your new institution.
   B. Recommend implementation of storage solutions based on what your previous institution did.
   C. Create a table of the ISMP best practice recommendations for the safe storage and handling of NMBs and compare with the current practice at your new institution.
   D. Survey the staff as to what they think the safest storage would be while still being convenient to obtain.

III. QUALITY ASSURANCE, QUALITY/PERFORMANCE IMPROVEMENT

A. Overview
1. Quality improvement (QI) consists of systematic and continuous actions that lead to measurable improvement in health care services and the health status of targeted patient groups.
2. An organization's quality is based on the current system (e.g., how things are currently done).
3. Health care performance is defined by an organization's efficiency, outcome of care, or level of patient satisfaction. Using benchmarks may help with measurements/goals/outcomes.
4. To achieve a different level of performance (i.e., results) and improve quality, an organization's current system needs to be challenged/evaluated.
5. Key components of a successful QI program:
    a. QI works as systems and processes.
    b. Keeps the intended outcome as the central focus
    c. Embraces a team approach
    d. Uses data to guide decision-making
    e. Focuses on processes versus specific people's actions
6. Improvement strategies
    a. Understand the delivery system and key processes.
    b. Recognize that resources (inputs) and activities carried out (processes), including the work around for the actual defined processes, are addressed together to ensure or improve the quality of care (outputs/outcomes).
7. Quality management or performance improvement departments within a health care institution often share data with risk and regulatory departments.
8. QI programs within an institution
    a. Executive steering committee
    b. Various departments involved in QI initiatives:
        i. Performance improvement
        ii. Pharmacy department
        iii. Nursing
        iv. Medical staff
        v. Respiratory
        vi. Quality department
        vii. Medical ethics committee
        viii. P&T committee
        ix. Data reporting
        x. Medication safety committee
        xi. Compliance department
        xii. Critical care/clinical specialty committee
9. Analyzing the quality assurance (QA)/QI program
    a. A normal level (upper and lower control limit) should be established for a process to operate.
    b. The process is evaluated, and the results are compared with the normal level expected. Control charts can show the variance of the output of a process over time. The process is considered *in control* if the variance between measurements is the normal random variation considered inherent in the process. If the variance falls outside the limits or has a run of non-natural points, the process is considered *out of control*.
    c. Example: Established process for daily sedative interruption for mechanically ventilated patients. The preestablished expected level of daily sedative interruption was established when the protocol was considered initiated. The QA data collected evaluate the frequency by which the assessments are being performed over a time interval.

B. Critical Care Pharmacist's Role in QI – Metrics for evaluating the quality of critical care pharmacy services
  1. ICU and hospital LOS
  2. ICU readmissions
  3. Impact on mortality or morbidity
  4. Impact on disease identification, disease prevalence, or clinical outcome
  5. Evaluation of infectious diseases within the ICU
  6. Cost of care versus diagnosis-related group (DRG) reimbursement
  7. Duration of mechanical ventilation
  8. Medication management procedures need to be continuously monitored and improved because of their complexity.
  9. Medication safety – Adverse drug events prevented, time since event reached a patient, etc.
  10. Direct costs (medication costs, technological upgrades, and software)
  11. Indirect costs (salaries, power for building)
  12. Data collection, analysis
  13. Implement processes to reduce medication costs and waste.

C. National Quality Initiatives
  1. The Institute of Medicine – Chartered in 1970. Published reports titled "The Urgent Need to Improve Health Care Quality," "Crossing the Quality Chasm," "To Err Is Human"
  2. The Institute for Healthcare Improvement (IHI) – Founded in 1991
     a. 100,000 Lives Campaign, 5 Million Lives Campaign (December 12, 2006 – December 9, 2008)
     b. No needless list
        i. No needless deaths
        ii. No needless pain or suffering
        iii. No helplessness in those served or serving
        iv. No unwanted waiting
        v. No waste
        vi. No one left out
     c. Critical care initiatives
        i. Acute myocardial infarction
        ii. Catheter-associated urinary tract infections
        iii. Central line–associated bloodstream infections
        iv. Health care–associated infections
        v. Sepsis detection and initial management
        vi. Medication reconciliation to prevent ADEs
        vii. Pain, agitation/sedation, delirium, immobility, and sleep (PADIS) (i.e., the ABCDEF bundle)
        viii. Surgical site infections
        ix. Ventilator-associated pneumonia
        x. Rapid response teams
        xi. High-alert medication safety
        xii. Pressure ulcer care
     d. The seven rights of medication administration: Right patient, right medication, right dose, right time, right route, right reason, right documentation.
     e. Ask "Why" five times to get to the root cause - key to solving a problem
  3. National Quality Forum – Created in 1999
     a. More than 300 measures, indicators, events, practices, and other products to help assess quality. Has been endorsed to become the gold standard of measuring health care quality

   b. Patient safety–endorsed measures notable for ICU care (2015)
      i. ADEs
      ii. Catheter-associated urinary tract infections
      iii. Central line–associated bloodstream infections
      iv. Surgical site infections
      v. Ventilator-associated pneumonia
      vi. Ventilator-associated events
      vii. Stroke
      viii. Acute myocardial infarction
      ix. Falls
      x. Pressure ulcer rate
   c. Health information technology–related safety events (2016)
   d. Harmonizing accountability in reporting and monitoring (2024).
      i. Aims to reduce preventable harm by first modernizing criteria for what constitutes a serious reportable event

4. The Leapfrog Group – Launched in 2000
   a. Hospital quality and safety survey is a voluntary survey of hospitals rating themselves on quality and safety practices
   b. Reported at www.leapfroggroup.org
   c. ICU-related measures
      i. CPOE
      ii. Bar code medication administration
      iii. ICU physician staffing
      iv. Hand hygiene
      v. Air embolism
      vi. Falls and Trauma
      vii. Central line–associated bloodstream infection
      viii. Catheter-associated urinary tract infection
      ix. Health-care associated infections including surgical site infection: Colon, methicillin-resistant *Staphylococcus aureus*, *Clostridioides difficile*
5. The Joint Commission (TJC) – Founded in 1951
   a. One of three CMS accreditation organizations, TJC is an independent, not-for-profit organization that sets the standards for accreditation in health care
   b. Tracer methodology – Method of evaluation done during an on-site survey that traces the health care experiences of a patient while in the hospital
   c. Identifies, tests, and specifies standardization of performance measures
   d. 2024 National Patient Safety Goals
      i. Identify patients correctly (NPSG.01.01.01).
         (a) Use at least two ways to identify patients. For example, use the patient's name and date of birth. This is done to make sure that each patient receives the correct medication and treatment.
      ii. Improve staff communication (NPSG.02.03.01).
         (a) Send important test results to the right staff person on time.
      iii. Use medications safely.
         (a) Before a procedure, label medications that are not labeled (e.g., medications in syringes, cups, and basins). Do this where medications and supplies are set up (NPSG.02.03.01).

            - (1) Unless an authorized staff member prepares a medication, takes it directly to the patient, and administers it without a break in the process, the medication must be labeled.
            - (2) Medication or solution labels should include name, strength, concentration, diluent and volume, and expiration date/time.
        - (b) Reduce the likelihood of patient harm associated with the use of anticoagulant therapy (NPSG.03.05.01)
        - (c) Record and pass along correct information about a patient's medications at admission, transfer, and discharge. Find out what medications the patient is taking. Compare these medications with new medications given to the patient. Make sure patients know which medications to take when they are at home. Tell patients it is important to bring their up-to-date list of medications each time they visit a physician (NPSG.03.06.01).
    - iv. Use alarms safely. Make improvements to ensure alarms on medical equipment are heard and responded to on time (NPSG.06.01.01).
    - v. Prevent infection (NPSG.07.01.01).
        - (a) Use the hand cleaning guidelines from the Centers for Disease Control and Prevention or the World Health Organization. Set goals for improving hand cleaning. Use the goals to improve hand cleaning.
    - vi. Identify patient safety risks: Reduce the risk of suicide (NPSG.15.01.01).
    - vii. Improve health care equity (NPSG16.01.01).
        - (a) Improving health care equity is a quality and patient safety priority. Identify health care disparities in the population and develop a written plan to improve this.
    - viii. Prevent mistakes in surgery using pre-procedural checklist:
        - (a) Make sure that the correct surgery is done on the correct patient and at the correct place on the patient's body (UP.01.01.01).
        - (b) Mark the correct place on the patient's body where the surgery is to be done (UP.01.02.01).
        - (c) Have a time-out before the surgery to make sure that a mistake is not being made and document the time-out (UP.01.03.01).
- e. The Joint Commission (TJC) chart-abstracted measures for hospitals. Note that beginning with 01/01/2020 discharges, the emergency department (ED), immunization (IMM), substance use (SUB), tobacco treatment (TOB), and venous thromboembolism (VTE) measures previously in the aligned CMS/TJC specifications manual have been moved to the *Specifications Manual for Joint Commission National Quality Measures* for hospital use.
    - i. Chart-abstracted measures from the hospital inpatient quality reporting (IQR) program; however, the hospital may still voluntarily report (critical care-focused measures)
        - (a) Venous thromboembolism - VTE-6-Hospital-acquired, potentially preventable venous thromboembolism
        - (b) Immunization - IMM-2 influenza immunization
    - ii. Required chart-abstracted core measures from the *Specifications Manual for Joint Commission National Quality Measures*, version 2022B2, posted 9/6/2022 (critical care–focused measures)
        - (a) Comprehensive stroke - CSTK-04 Procoagulant reversal agent initiation for intracerebral hemorrhage (ICH)
        - (b) Comprehensive stroke - CSTK-05a Hemorrhage transformation for patients treated with intravenous alteplase therapy only
        - (c) Comprehensive stroke - CSTK-05b Hemorrhage transformation for patients treated with intravenous alteplase therapy or mechanical endovascular reperfusion therapy
        - (d) Comprehensive stroke - CSTK-06 Nimodipine treatment administered

        (e) Comprehensive stroke - CSTK-08 Thrombolysis in cerebral infarction (TICI) post-treatment reperfusion grade
        (f) Emergency department - ED-1a - Median time from ED arrival to ED departure for admitted ED patients
        (g) Emergency department - ED-2a - Admit decision time to ED departure time for admitted patients
        (h) Stroke - STK-01 Venous thromboembolism (VTE) prophylaxis
        (i) Stroke - STK-02 Discharged on antithrombotic therapy
        (j) Stroke - STK-03 Anticoagulation therapy for atrial fibrillation/flutter
        (k) Stroke - STK-04 thrombolytic therapy
        (l) Stroke - STK-05 antithrombotic therapy by end of hospital day 2
        (m) Stroke - STK-06 discharged on statin medication
        (n) Stroke - STK-08 stroke education

6. Det Norske Veritas (DNV) – Established in 2008:
    a. One of three CMS-approved hospital accreditation organizations.
    b. Over 600 hospitals have converted from TJC to DNV.
    c. DNV does not set any standards for quality, but allows the hospital leadership to develop quality initiatives (e.g., marking the surgical site is a TJC standard).
    d. If the institution is accredited by the DNV, the hospital leadership establishes these standards.
7. Healthcare Facilities Accreditation Program (HFAP)
    a. One of three CMS-approved hospital accreditation organizations, the HFAP was originally created in 1945 to conduct objective review of services provided by osteopathic hospitals.
    b. Provides accreditation to all hospitals, ambulatory care/surgical facilities, mental health facilities, physical rehabilitation facilities, clinical laboratories and critical access hospitals. HFAP also provides certification reviews for primary stroke centers.
    c. Standards are written and cross-walk written tied directly to the Medicare requirements.
8. AHRQ (Agency for Healthcare Research and Quality) – The health services research arm of the U.S. Department of Health and Human Services. Sponsors the National Quality Measures Clearinghouse – A “public repository for evidence-based quality measures and measure sets”
9. Hospital Quality Alliance – Created in 2002
    a. Hospital Compare was created through the efforts of Medicare and the Hospital Quality Alliance
    b. 2004 – Hospitals could voluntarily report data on 10 “starter-set” quality performance measures and receive incentive payment.
    c. 2005 – Quality-of-care data expanded to 21 measures
    d. 2008 – Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) – First national, standardized, publicly reported survey of patients’ perspectives of hospital care
    e. Reporting initiatives sharpens the focus on QI.
10. CMS
    a. Mission – To “ensure effective up-to-date health care coverage and to promote quality care for beneficiaries”
    b. Quality initiative (established in 2001) empowers consumers with quality-of-care information and encourages providers to improve the quality of care.
    c. Hospital quality initiative (established in 2003) – Hospitals must submit data measures or accept a reduction in payment.
        i. Pay-for-performance measures associated with quality measures
        ii. CMS has removed many previously reportable core measures; however, the institution can choose which previously required measures to report.
        iii. FY 2026 Payment Determination Hospital IQR Program Measures (selected measures)

Table 1. Selected CMS Hospital IQR Program Measures for FY 2026 Payment Update

Topic	Measure
Stroke Measure (STK) Set	
	• Discharged on antithrombotic therapy (STK-02) • Anticoagulation therapy for atrial fibrillation/flutter (STK-03) • Antithrombotic therapy by the end of hospital day 2 (STK-05)
Venous Thromboembolism (VTE) Measure Set	
	• Venous thromboembolism prophylaxis (VTE-1) • Intensive Care Unit Venous Thromboembolism Prophylaxis (VTE-2)
Sepsis Measure	
	• Severe sepsis and septic shock: Management bundle (SEP-1 Composite Measure)
Mortality Measures	
	• Hospital 30-Day, All-cause, Risk-Standardized Mortality Rate following Acute Ischemic Stroke (MORT-30-STK)
Readmission Measures	
	• Excess Days in Acute Care after Hospitalization for Acute Myocardial Infarction (AMI Excess Days) • Excess Days in Acute Care after Hospitalization for Heart Failure (HF Excess Days) • Excess Days in Acute Care after Hospitalization for Pneumonia (PN Excess Days)
Safe Use of Opioids	
	• Safe Use of Opioids – Concurrent Prescribing
CMS PSI 04	
	• Death rate among surgical inpatients with serious treatment complications
Hospital Harm	
	• Severe hypoglycemia (HH-01) • Severe hyperglycemia (HH-02) • Opioid-related adverse events (HH-ORAE)

CMS = Centers for Medicare & Medicaid Services; FY = fiscal year; IQR = inpatient quality reporting.

Information from: Centers for Medicare & Medicaid Services (CMS). CMS Measures Inventory Tool. Available at https://www.qualityreportingcenter.com/globalassets/2024/01/iqr/01.-iqr_fy-2026_cms-measures_vfinal508.pdf

11. Institute for Safe Medication Practices (ISMP) – Established 1975
    a. Nonprofit organization responsible for targeting medication error prevention and safe medication use; a certified patient safety organization
    b. Based on a nonpunitive approach and system-based solutions
    c. Five key areas of focus: Knowledge, analysis, education, collaboration, and communication
    d. Medication Errors Reporting Program – Practitioner self-reporting program
    e. ISMP Quarterly Action Agenda and Bi-weekly Safety Alerts
        i. Can review bi-weekly and conduct gap analysis to proactively identify at-risk safety concerns.
        ii. All bi-weekly newsletters are combined into a quarterly action agenda to review and identify areas for opportunity to improve safety in medication use processes.
    f. ISMP Targeted Medication Safety Best Practices for Hospitals (2024–2025)
        i. Worksheet can be used to perform a gap analysis of an institution's performance with medication safety issues that continue to cause fatal and harmful errors to patients.
        ii. The interactive worksheet can be found at https://www.ismp.org/resources/worksheet-ismp-targeted-medication-safety-best-practices-hospitals.

12. The Choosing Wisely initiative of the American Board of Internal Medicine Foundation was a collaboration of critical care societies including the American Association of Critical Care Nurses, American College of Chest Physicians, American Thoracic Society, and Society of Critical Care Medicine. The goal was to drive conversations between clinicians and patients about what procedures, tests, and treatments are truly needed. The 11-year campaign ended in 2023. The Choosing Wisely campaign identified many examples; however, these are now encouraged to be emphasized through specialty societies for publication of these lists. The campaign website still emphasizes the following for patient advocacy to ask questions of their care team:
    a. Do I really need this test/procedure?
    b. What are the risks?
    c. Are there simpler, safer options?
    d. What happens if I don't do anything?
    e. How much does it cost?

Patient Case

3. You are reviewing compliance with the national patient safety goals in the perioperative setting specific to appropriate medication labeling. Through observation, you notice that there are inconsistencies in how propofol is drawn up and labled in the syringe, if labeled at all. In the majority of cases, the name of the drug is placed on the label. What other information should be included on the label of the syringe?
    A. Patient name, drug name, dose, and expiration date/time.
    B. Drug name, concentration, diluent if applicable, and expiration date/time.
    C. Patient name, drug name, drug dose, and concentration.
    D. Drug name, drug dose, concentration, and diluent if applicable.

D. The goal of the ASHP Practice Advancement Initiative (PAI) is to significantly advance the health of patients by supporting futuristic practice models that support the most effective use of pharmacists as direct patient care providers. The initiative aims to assist leaders and practitioners in creating a framework, determining services, identifying emerging technology, developing templates, and implementing change. The ASHP Pharmacy Practice Model Initiative started in 2010. See Figure 1 for the Practice Advancement Initiative 2030 recommendations.

E. Local Quality Initiatives (from ASHP: The ASHP Discussion Guide on the Pharmacist's Role in Quality Improvement)
    1. Every accredited hospital must participate in QI initiatives.
    2. The overall goals of the PI programs are to maintain and support the delivery of safe, quality care.
    3. Each program should include the following:
        a. Adherence to standards of care
        b. Opportunities for improvement, with action plans to implement change strategies
        c. Strategies for the effectiveness of change strategies
        d. Involvement of multidisciplinary teams in process improvement
    4. PI plans should:
        a. Articulate the commitment to PI
        b. Delineate the goals of the PI process
        c. Specify the authority and responsibilities for PI
        d. Describe the organizational structure and process related to the PI program
        e. Describe the method for improving organizational performance
        f. Describe the communication and recognition of PI activities

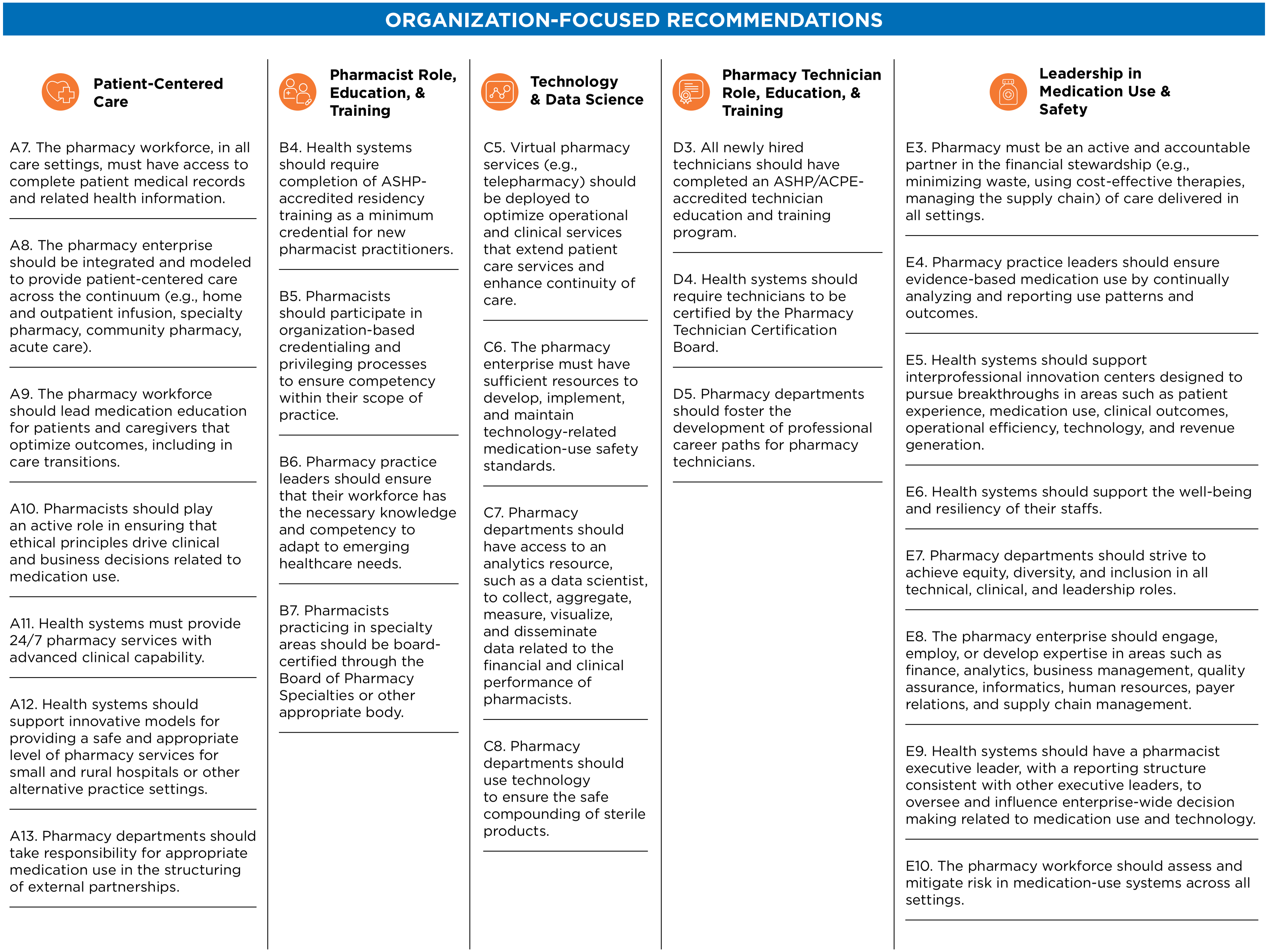
The goal of PAI 2030 is to significantly advance the health and well-being of people by supporting patient-centered care delivery models that optimize the most effective use of pharmacists as direct patient care providers.

PRACTICE-FOCUSED RECOMMENDATIONS

Patient-Centered Care	**Pharmacist Role, Education, & Training**	**Technology & Data Science**	**Pharmacy Technician Role, Education, & Training**	**Leadership in Medication Use & Safety**
A1. Pharmacists should collaborate with patients, families, and caregivers to ensure that treatment plans respect patients' beliefs, values, autonomy, and agency.	B1. All pharmacists should have an individualized continuing professional development plan.	C1. Pharmacists should use health information technologies to advance their role in patient care and population health.	D1. Pharmacy technicians should participate in advanced roles in all practice settings to promote efficiency and improve access to patient care.	E1. Pharmacists should advance the use of pharmacogenomic information for personalized medication treatment.
A2. The pharmacy workforce should lead medication reconciliation processes during care transitions (e.g., emergency department, upon admission and discharge, ambulatory care setting, community pharmacy, long term care).	B2. Pharmacists should leverage and expand their scope of practice, including prescribing, to optimize patient care.	C2. Pharmacy practice leaders should foster the development and application of advanced analytics (e.g., machine learning and artificial intelligence) in activities such as risk assessment, monitoring performance metrics, identifying patients in need of pharmacist care, optimizing medication use, and business management.	D2. Pharmacy technicians should have complete responsibility for advanced technical and supporting activities (e.g., order fulfillment, tech-check-tech, regulatory compliance, supply chain management, diversion prevention, revenue cycle management, patient assistance programs).	E2. Pharmacists should assume leadership roles in medication stewardship activities at the local, state, and national levels.
A3. The pharmacy workforce should collaborate with patients, caregivers, payers, and healthcare professionals to establish consistent and sustainable models for seamless transitions of care.	B3. Pharmacists should participate in and assume key roles on emergency response teams.	C3. Pharmacy practice leaders should be engaged in assessing emerging patient care technologies (e.g., mobile applications, monitoring devices, digital wearables or ingestables, blockchain technology) to support optimal medication-use outcomes.		
A4. Pharmacist documentation related to patient care must be available to all members of the healthcare team, including patients, in all care settings.		C4. The pharmacy workforce should be competent in health information technology (including but not limited to analytics, automation, and clinical applications of technology) with ongoing education and training embedded at all stages of career development.		
A5. The pharmacy workforce should partner with patients and the interprofessional care team to identify, assess, and resolve barriers to medication access, adherence, and health literacy.				
A6. Patients must have access to a pharmacist in all settings of care.				

Figure 1. ASHP Practice Advancement Initiative 2030.

Used with permission from: American Society of Health-System Pharmacists (ASHP). PAI 2030 Recommendations. Available at https://www.ashp.org/Pharmacy-Practice/PAI/PAI-Recommendations.



ORGANIZATION-FOCUSED RECOMMENDATIONS

Patient-Centered Care

A7. The pharmacy workforce, in all care settings, must have access to complete patient medical records and related health information.

A8. The pharmacy enterprise should be integrated and modeled to provide patient-centered care across the continuum (e.g., home and outpatient infusion, specialty pharmacy, community pharmacy, acute care).

A9. The pharmacy workforce should lead medication education for patients and caregivers that optimize outcomes, including in care transitions.

A10. Pharmacists should play an active role in ensuring that ethical principles drive clinical and business decisions related to medication use.

A11. Health systems must provide 24/7 pharmacy services with advanced clinical capability.

A12. Health systems should support innovative models for providing a safe and appropriate level of pharmacy services for small and rural hospitals or other alternative practice settings.

A13. Pharmacy departments should take responsibility for appropriate medication use in the structuring of external partnerships.

Pharmacist Role, Education, & Training

B4. Health systems should require completion of ASHP-accredited residency training as a minimum credential for new pharmacist practitioners.

B5. Pharmacists should participate in organization-based credentialing and privileging processes to ensure competency within their scope of practice.

B6. Pharmacy practice leaders should ensure that their workforce has the necessary knowledge and competency to adapt to emerging healthcare needs.

B7. Pharmacists practicing in specialty areas should be board-certified through the Board of Pharmacy Specialties or other appropriate body.

Technology & Data Science

C5. Virtual pharmacy services (e.g., telepharmacy) should be deployed to optimize operational and clinical services that extend patient care services and enhance continuity of care.

C6. The pharmacy enterprise must have sufficient resources to develop, implement, and maintain technology-related medication-use safety standards.

C7. Pharmacy departments should have access to an analytics resource, such as a data scientist, to collect, aggregate, measure, visualize, and disseminate data related to the financial and clinical performance of pharmacists.

C8. Pharmacy departments should use technology to ensure the safe compounding of sterile products.

Pharmacy Technician Role, Education, & Training

D3. All newly hired technicians should have completed an ASHP/ACPE-accredited technician education and training program.

D4. Health systems should require technicians to be certified by the Pharmacy Technician Certification Board.

D5. Pharmacy departments should foster the development of professional career paths for pharmacy technicians.

Leadership in Medication Use & Safety

E3. Pharmacy must be an active and accountable partner in the financial stewardship (e.g., minimizing waste, using cost-effective therapies, managing the supply chain) of care delivered in all settings.

E4. Pharmacy practice leaders should ensure evidence-based medication use by continually analyzing and reporting use patterns and outcomes.

E5. Health systems should support interprofessional innovation centers designed to pursue breakthroughs in areas such as patient experience, medication use, clinical outcomes, operational efficiency, technology, and revenue generation.

E6. Health systems should support the well-being and resiliency of their staffs.

E7. Pharmacy departments should strive to achieve equity, diversity, and inclusion in all technical, clinical, and leadership roles.

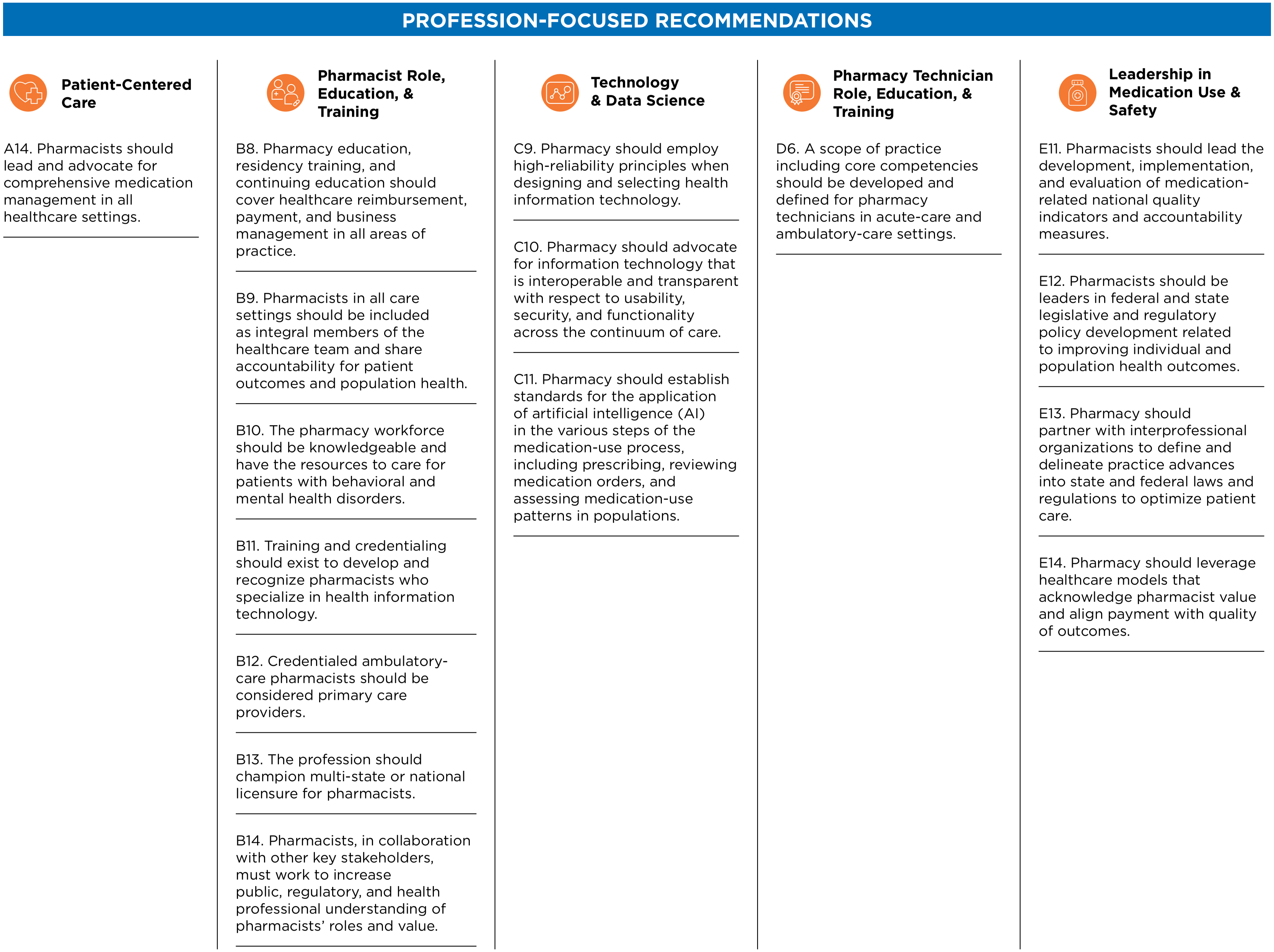
E8. The pharmacy enterprise should engage, employ, or develop expertise in areas such as finance, analytics, business management, quality assurance, informatics, human resources, payer relations, and supply chain management.

E9. Health systems should have a pharmacist executive leader, with a reporting structure consistent with other executive leaders, to oversee and influence enterprise-wide decision making related to medication use and technology.

E10. The pharmacy workforce should assess and mitigate risk in medication-use systems across all settings.

Figure 1. ASHP Practice Advancement Initiative 2030. (*continued*)

Used with permission from: American Society of Health-System Pharmacists (ASHP). PAI 2030 Recommendations. Available at https://www.ashp.org/Pharmacy-Practice/PAI/PAI-Recommendations.



PROFESSION-FOCUSED RECOMMENDATIONS

Patient-Centered Care	Pharmacist Role, Education, & Training	Technology & Data Science	Pharmacy Technician Role, Education, & Training	Leadership in Medication Use & Safety
A14. Pharmacists should lead and advocate for comprehensive medication management in all healthcare settings.	B8. Pharmacy education, residency training, and continuing education should cover healthcare reimbursement, payment, and business management in all areas of practice.	C9. Pharmacy should employ high-reliability principles when designing and selecting health information technology.	D6. A scope of practice including core competencies should be developed and defined for pharmacy technicians in acute-care and ambulatory-care settings.	E11. Pharmacists should lead the development, implementation, and evaluation of medication-related national quality indicators and accountability measures.
	B9. Pharmacists in all care settings should be included as integral members of the healthcare team and share accountability for patient outcomes and population health.	C10. Pharmacy should advocate for information technology that is interoperable and transparent with respect to usability, security, and functionality across the continuum of care.		E12. Pharmacists should be leaders in federal and state legislative and regulatory policy development related to improving individual and population health outcomes.
	B10. The pharmacy workforce should be knowledgeable and have the resources to care for patients with behavioral and mental health disorders.	C11. Pharmacy should establish standards for the application of artificial intelligence (AI) in the various steps of the medication-use process, including prescribing, reviewing medication orders, and assessing medication-use patterns in populations.		E13. Pharmacy should partner with interprofessional organizations to define and delineate practice advances into state and federal laws and regulations to optimize patient care.
	B11. Training and credentialing should exist to develop and recognize pharmacists who specialize in health information technology.			E14. Pharmacy should leverage healthcare models that acknowledge pharmacist value and align payment with quality of outcomes.
	B12. Credentialed ambulatory-care pharmacists should be considered primary care providers.			
	B13. The profession should champion multi-state or national licensure for pharmacists.			
	B14. Pharmacists, in collaboration with other key stakeholders, must work to increase public, regulatory, and health professional understanding of pharmacists' roles and value.			

Figure 1. ASHP Practice Advancement Initiative 2030. (*continued*)

Used with permission from: American Society of Health-System Pharmacists (ASHP). PAI 2030 Recommendations. Available at https://www.ashp.org/Pharmacy-Practice/PAI/PAI-Recommendations.

F. ASHP Standardize 4 Safety Initiative
  1. ASHP received funding from the FDA on this interprofessional effort.
  2. Goal is to standardize medication concentrations to reduce errors, especially during transitions of care.
  3. Focus is on both intravenous and oral liquid medications for patients of all ages and all settings.
  4. Standardized concentration lists have been established. Hospitals and health care systems are encouraged to adopt these standardized concentrations.
  5. These lists can be downloaded or use the interactive worksheet to assess your organization's progress to meet this goal.

G. QI Tools
  1. Six Sigma – DMAIC process: Goal to reduce variation around process defects and test with statistical methods
    a. DEFINE the problem
    b. MEASURE current state through process mapping, or Failure Modes and Effects Analysis (FMEA)
    c. ANALYZE relationship between input/output
    d. IMPROVE future state processes
    e. CONTROL to sustain the gain
  2. Failure Modes and Effects Analysis (FMEA): Prospective evaluation to determine possible failures in processes in order to prevent them from occurring on initiation
    a. Evaluate the steps in the process
    b. What could go wrong? (Failure modes)
    c. Why would the failure happen? (Failure causes)
    d. What would be the consequences of each failure? (Failure effects)
  3. LEAN principles: How do we do more with less? Ideally, create a high-quality service/product with less resources or a shorter lead time
    a. Value - Activity that enhances service from the customer's viewpoint
      i. Waste – opposite of value with goal to eliminate waste
      ii. Types of waste: Defects, Overproduction, Waiting, Not using employees' creativity, Transport, Inventory, Motion, Extra Processing ("DOWNTIME")
    b. Value stream – all actions required to bring service to the customer (both value and non-value added)
      i. Value stream mapping is a LEAN tool that can be used to "walk the line" by experiencing the process and defining the current state.
    c. Flow – flow of processes without interruption
      i. Process mapping to outline the workflow
    d. Pull – trigger flow from demand
    e. Perfection – continuous improvement
  4. Plan-do-study-act (PDSA): Model for promoting quality improvement through real-time evaluation of standard work
    a. What are we trying to accomplish? – An aim or project goal must be developed (example of specific aim: time to appropriate antibiotic therapy in patients seen in the ED with presumed sepsis).
      i. Describe the process to be improved.
      ii. Set a target for improvement that extends beyond current performance.
      iii. Secure necessary resources in the process.
    b. How will we know that a change is an improvement?
      i. Establish baseline measurement – Select and gather data.
      ii. Compare baseline data with the target and identify key causes and sources of variation.

    c. What changes can we make that will result in improvement?
        i. Broad, general ideas and thoughts about change (“change concepts”)
        ii. Select the change.
    d. Testing change
        i. Scientific method
    e. Plan-do-study-act cycle: Use an A3, which is a visual management system to identify opportunities for improvement to ensure they align with system goals. A3 was developed by Toyota to communicate with as few words as possible.
        i. Plan – Analyze the problem or opportunity and search for the root cause. Design the process improvement and implementation plan.
            (a) Questions are asked and predictions are made.
            (b) Details are described.
            (c) Who will make the test?
            (d) What exactly will they do?
            (e) When will they do it?
            (f) Where will they do it?
            (g) How long will they do it?
            (h) Predict what will happen.
            (i) Determine which data to collect.
        ii. Do – try it out
            (a) Change is tested following the “plan.”
            (b) Collect data on the change.
            (c) Unexpected problems and observations are documented.
        iii. Study – analyze data, study results
            (a) Study the effect of the test change on the single measure.
            (b) Compare data with predictions.
            (c) Summarize what was learned.
        iv. Act – refine the change on the basis of what was learned
            (a) Adapt, adopt, or abandon change idea for next cycle.
            (b) Develop an implementation plan.
            (c) Share final reflections.

H. Data Generation
1. Benchmarking – Compares your performance with that of another health care system or a database of collective health care system performance
2. Provider concerns
3. Nursing reports/concerns
4. Patient concerns or comments: Reports from third-party payers and regulatory agencies
5. Incident reporting
6. Root-cause analysis reports
7. Medication error reports
8. Patient care evaluation studies
9. Patient satisfaction survey results
10. CPOE use reports
11. Bar code medication administration data reports
12. Continuous infusion smart pump integration data reports
    a. Include pump integration data reports if implemented

I. Analysis Tool Kit
  1. Affinity diagrams
  2. Cause-and-effect diagrams
  3. Decision matrixes
  4. Root-cause analysis
  5. Apparent cause analysis
  6. Process maps
  7. Run chart, control chart, or flowcharts
  8. Force-field analysis
  9. Histograms, scatterplots
  10. Relationship diagrams
  11. Supplier, input, process, output, customer
  12. Voice of the customer
  13. Five Whys
  14. Fishbone diagram
  15. FMEA

J. Reporting and Publishing QI Results
  1. Report QI data internally to trend and track progress and share work that is being accomplished.
  2. Important to publish QI data to promote improvement efforts in health care
  3. Reduces the chances of the same mistakes being repeated
  4. Shares your work by spreading important and useful information
  5. Standards for Quality Improvement Reporting Excellence (SQUIRE) – Provides a framework for reporting new knowledge about how to improve health care. Available at www.squire-statement.org/

Patient Cases

4. As a critical care pharmacist, you are involved in a QI program. Which TJC measure is best known to be affected by the critical care pharmacist?
   A. ED median time from ED arrival to ED departure for admitted ED patients.
   B. Procoagulant reversal agent initiation for intracerebral hemorrhage (ICH).
   C. Hemorrhagic transformation for patients receiving intravenous alteplase therapy or mechanical endovascular reperfusion therapy.
   D. Severe sepsis and septic shock management bundle.

5. As part of a QI initiative, you identify an increase in the monthly rate of catheter-related bloodstream infections in your ICU. You decide to evaluate the current practice using LEAN methodology. Which is the best example of a component of LEAN?
   A. Define the problem.
   B. Ask your nurses why they think a spike in catheter-related bloodstream infections has occurred.
   C. Identify transportation barriers.
   D. Describe the past process.

IV. MEDICATION USE EVALUATION

A. TJC requires medication use evaluations (MUEs) to be completed to monitor the safety of medications. ASHP published guidelines on performing a MUE in 2021.

B. MUEs and DUEs are often used synonymously. Both DUEs and MUEs are PI and QA methods that ensure optimal medication therapy management and improve patient safety and outcomes.

C. A DUE is drug- or disease-specific, focusing specifically on the criteria-based assessment of the medication use process and prescribing, whereas an MUE provides a broader scope that focuses on a drug or class of drugs, the process(es), and the outcome, with a specific emphasis on improving patient outcomes. MUEs focus on several elements of the medication process/use such as prescribing, pharmacist medication order validating or verifying, dispensing, preparing, administering, monitoring, patient education, and outcomes.

D. ASHP Guidelines on MUEs: Include a performance improvement framework to improve safety, efficacy, quality, and efficiency in patient care.
  1. An example of a performance improvement framework is FOCUS-PDSA:
    a. Find the process to be targeted for improvement.
    b. Organize the team that knows the process.
    c. Clarify current knowledge of the process.
    d. Understand causes of process variation.
      i. Five Whys: Ask “why” five times to get to the root cause.
    e. Select process improvement.
      i. FACES (feasibility, acceptability, cost/benefit, effectiveness, sustainability) tool
    f. Plan: Develop a solution.
    g. Do: Implement improvements.
    h. Study: Evaluate the results.
    i. Act: Determine the changes needed moving forward and implement them.

E. The sample size of the MUE depends on the type of medication data being analyzed—usually, a sample of 20–30 patients is sufficient; however, a sample of 100 or more patients may be required to analyze patient outcomes. The primary determinant of sample size will be the threshold level. An infrequent failure to meet the specified criteria (less than 5%) will require a large population sample size (greater than 200). If there is a frequent failure to meet criteria (25%–50%) a smaller sample size can be used (30–60).

F. Critical thresholds should be set to evaluate the level of noncompliance in the process that would trigger action (i.e., quality improvement).

G. Data collection for specific criteria can use either a yes/no format (with a section for comments) or open-ended questions. Using CPOE and electronic medical records, the processes of data retrieval, monitoring, and generating specialized reports have become easier.

H. The type and number of MUEs should be determined by the risk mitigated when using a medication. Broad categories for MUEs include:
  1. Promote optimal medication therapy
  2. Improve patient safety
  3. Standardize to reduce unnecessary variation
  4. Optimize drug therapy

5. Assess value of innovative practices
6. Meet quality or regulatory standards
7. Minimize costs
   a. These should be considered together with the impact of the medication or medication use process on patients and the medication use system as a whole to prioritize the highest-impact MUEs.

I. Medications selected for an MUE may be based on the following:
   1. High risk
   2. High volume
   3. ADEs
   4. Preventable ADEs
   5. Near-miss and harmful medication errors
   6. Formulary review, including addition (non-formulary use), retention, or deletion
   7. Pharmacy intervention data
   8. Treatment failures
   9. Physician or nurse identification or request
   10. Patient concerns
   11. Off-label use
   12. High cost
   13. Beneficial when used a specific way
   14. Drug shortages, recalls, or safety alerts

J. Examples of medication use processes in critically ill patients that may be selected for an MUE can be found in Box 1.

K. Ideally, MUEs should be performed proactively and used to identify any gaps in practice or patient safety.
   1. An *interventional MUE* is completed concurrently or prospectively, and if the criteria are not met, an intervention by the pharmacist should be made to improve the use of the medication and patient outcomes.
   2. A *noninterventional MUE* is completed concurrently or retrospectively by a medical record review, and data are collected but criteria are not met. The review is retrospective, and there is no pharmacist-to-prescriber interaction during the review process.

L. MUEs should have specific criteria set – These criteria are best determined by a multidisciplinary team of medication or disease experts.

M. MUE criteria may be approved by the P&T committee. The P&T committee may create an MUE subcommittee. Other hospital committees such as the QI committee may also request that an MUE be performed. Other names for the MUE committees may include formulary, drug safety, therapeutic assessment, medication safety, and drug use review committees.

N. The MUE subcommittee should be multidisciplinary and may be composed of the following:
   1. Clinical pharmacists
   2. Physicians, nurse practitioners, and physician assistants
   3. Nurses
   4. Administrators
   5. PI/QA representatives
   6. Risk management representatives
   7. Respiratory therapists, nutritionists, and other ancillary support staff

Box 1. Examples of High-Risk Medication-Related Processes Suited for an MUE in Critically Ill Patients

PADIS (ABCDEF bundle) protocols
Use of neuromuscular blocking agents
Alcohol withdrawal management
Management of supratherapeutic anticoagulation (e.g., warfarin, direct oral anticoagulants, heparin, direct thrombin inihibitors)
Use of β-blockers in myocardial infarction
Monitoring for dysrhythmias with QTc-prolonging drugs
Antihypertensive IV-to-PO switch therapy
Antihypertensive use in acute stroke
Fluid resuscitation
Management of gastrointestinal bleeding
Use of total parenteral nutrition
Use of albumin
Hyperkalemia management guidelines
Hypomagnesemia management guidelines
Management of status epilepticus
Management of hyponatremia
Use of IV sodium bicarbonate
Vancomycin dosing and ordering serum concentrations
Aminoglycoside dosing and ordering serum concentrations
Intermittent infusions of antimicrobials (e.g., carbapenems, piperacillin/tazobactam)
Evaluation of antimicrobial dosing in CRRT or hemodialysis
Surgical prophylaxis guidelines
Antimicrobial IV-to-PO switch therapy
Management of *Clostridioides difficile* diarrhea
Vaccine administration
IV push medication guidelines (rate of administration and medication preparation - diluted or undiluted)
Stress ulcer prophylaxis
Insulin infusions
Hypoglycemic protocols

CRRT = continuous renal replacement therapy; PO = oral(ly); QTc = corrected QT (interval).

O. Given the pharmacist's expertise in medication management, pharmacists often chair or co-chair the MUE subcommittee and perform the MUE.

P. The MUE subcommittee can recommend drugs and drug processes that require an MUE to the P&T committee; alternatively, the P&T committee can request MUEs from the MUE subcommittee.

Q. The MUE process includes reviewing the findings and developing plans of improvement. The results and conclusions of the MUE should be reported to the P&T committee and department chairs.

R. After plans for improvement are identified and actions taken, a follow-up MUE should be completed to document that improvement has occurred.

S. Periodic MUEs in the same area should be performed every 3–6 months for 1 year to ensure that the improvements made remain effective and are sustained. If any new changes have occurred in the medication use process, the MUE criteria should be reassessed and the new criteria incorporated.

T. Policies and educational initiatives should be developed to improve opportunities identified from the MUE, such as:
  1. In-service lectures
  2. Newsletter publications
  3. Medication alerts
  4. Guideline development
  5. Protocols
  6. Policy and procedures
  7. CPOE pathways, prescribing guides, or information or pop-up warnings

Patient Case

6. Which medication use process is best suited for an MUE?
  A. Review of pharmacist notes in the electronic health record (EHR).
  B. Review of accuracy of expiration dates placed on intravenous admixture products.
  C. Review of vancomycin dosing and ordering of vancomycin blood concentrations.
  D. Review of frequency of drug interaction warnings on the CPOE system.

V. DOCUMENTATION PROCESSES USED FOR CRITICAL CARE PHARMACY SERVICES

A. Importance of Documentation
  1. Evidence of economic benefit and improvement in patient safety for clinical pharmacy services (CPS) and critical care pharmacy services is well established. The Society of Critical Care Medicine supports an ICU pharmacist as an essential component of the ICU team.
  2. Clinical pharmacy interventions that affect patient care should be documented in the electronic medical record. Pharmacist involvement directly optimizes the use of medications, decreases drug-related costs, prevents adverse effects, improves quality and efficacy of care, reduces mortality, shortens length of stay (LOS), and lowers overall patient care costs.
  3. Clinical interventions that can be performed by a critical care pharmacist may include but are not limited to:
    a. Optimization of the correct drug for the disease process (inappropriate therapy, duplication of therapy, therapy no longer needed, etc.)
    b. Optimization of the correct dose based on the patient's end organ function, including continuous renal repacement therapy adjustments, hepatic dose adjustments, and dose adjustments needed during extracorporeal membrane oxygenation
    c. Anticoagulation adjustment
    d. Antibiotic optimization (deescalation, bug-drug mismatch, duration of therapy, etc.)
    e. Intravenous to oral conversion
    f. Transitions of care and/or medication reconciliation
    g. Pharmacokinetic dosing
    h. Adverse event management
    i. Drug-drug or drug-disease management
    j. Ensuring adherence to ICU medication therapy protocols (i.e., alcohol withdrawal, PADIS management, neuromuscular blockade, etc.)
    k. Drug and laboratory monitoring

4. Additionally, critical care pharmacist interventions may identify opportunities for protocol or guideline development or may identify opportunities for an MUE to be completed.
5. Documenting CPS is important not only to quantify CPS and workload, but also to provide justification for maintaining and expanding services.
6. CPS should be evaluated for cost impact and cost outcomes savings and should include the following:
   a. Weighted metric for each variable to quantify measured activities
      i. One way to add impact to each intervention is by using the Overhage and Lukes Scale to capture severity of interventions.
   b. Pharmacotherapy improvement
   c. Cost savings or cost avoidance
   d. Antibiotic stewardship
   e. Provider education
   f. Quality/safety improvement (value-based purchasing, HCAHPS)
   g. Participation in emergency response (cardiac arrest, stroke, sepsis)
   h. Prospective chart review
   i. Rounding with health care providers
   j. Formal pharmacy consults
7. Collaborative drug therapy management (CDTM) or collaborative practice agreements (CPAs) – When a prescriber and a pharmacist establish written guidelines or protocols authorizing the pharmacist to initiate, modify, or continue drug therapy for a specific patient. CDTM is a type of pharmacotherapeutic intervention that should be documented and reported. Examples relevant to the practice of critical care pharmacy include parenteral nutrition prescribing, antimicrobial stewardship programs, and analgesia/sedation/delirium screening and management.

Patient Case

7. You round daily in your ICU as part of the multidisciplinary team. Your manager asks you to help them justify clinical pharmacy services to obtain additional FTEs for the other ICUs at your institution. Which of the following would be the most effective metrics to include in the justification to hospital leadership?
   A. Antibiotic stewardship and cost savings.
   B. Provider education and in-services provided.
   C. Time spent rounding and on other activities.
   D. Renal dose adjustments and intravenous to oral conversion.

B. Documentation Process
   1. The pharmacy department should have a policy and procedure for documenting clinical pharmacy interventions. In addition, a dashboard should be developed that incorporates these clinical interventions and shared with key stakeholders (Appendix 2).
   2. In general, pharmacist interventions are the result of either formal or informal consultations or unsolicited interventions.
   3. Documenting the pharmacotherapeutic intervention and plan in the EHR provides transparency between all health care professionals – physicians, nurses, pharmacists, dietitians, respiratory therapists, and social workers and provides written documentation of recommended changes.
   4. Pharmacists can also document interventions in the pharmacy profile; however, this method generally allows for review only by pharmacy personnel who have access to the pharmacy computer system such as other pharmacists and pharmacy interns, students, and technicians.

5. Both methods should be available for documenting pharmacotherapeutic interventions, and criteria should be established to determine which method is most appropriate.
6. Pharmacists should have the authority to document pharmacotherapeutic interventions in the EHR.
7. Pharmacists should be trained and educated to document in the EHR. The ASHP Clinical Skills Certificate program is a tool that can be used to train pharmacists to document in the EHR.
8. Documentation methods may include standard format documentation methods such as:
   a. SOAP (subjective, objective, assessment, plan)
   b. TITRS (title, introduction, text, recommendation, signature)
   c. FARM (findings, assessment, resolution, monitoring)
9. Wording for solicited consultations should be direct. Unsolicited pharmacist interventions should be documented subtly, allowing the primary provider to decline the recommendation without incurring liability. Phrases that can be used include:
   a. "May consider"
   b. "Suggest"
   c. "May recommend"
10. When feasible, written notes by pharmacists should be documented in the EHR after an oral communication with the clinician; this allows for any patient data discrepancies to be corrected and for agreement and confirmation between the prescriber and the pharmacist to execute the intervention.
11. Pharmacists should follow up on their patient interventions daily and provide follow-up notes that include patient progress or new interventions, when needed.
    a. Pharmacists should provide their contact information.
    b. Co-signatures should be required for pharmacy residents (until deemed competent according to pharmacy department standards), interns, and students.
    c. Continual physical presence during and after direct patient care rounds should be provided to support the physicians, advanced practice providers, and nursing team with triaging medication-related questions.
12. Many web-based or handheld electronic systems are available that can be used to document and report pharmacotherapeutic interventions and cost savings. Ideally, these are documented in the patient's EHR for the reporting of weighted metrics.

Patient Case

8. During ICU rounds, the team is recommending a cost-prohibitive non-formulary drug with controversial outcomes as a last line vasopressor for a patient with septic shock. You review the chart and think there are safer formulary options to try before resorting to this new therapy. You are required to document your interventions in the patient chart for tracking purposes. Which wording is the most appropriate to use?
   A. Because of the significant cost of this drug, the team should resort to other formulary options.
   B. This drug was associated with significant adverse effects in clinical trials and will likely cause harm if used in this patient.
   C. The team should consider optimizing the patient's pharmacological therapy with agents that are on formulary and have a proven benefit in patients with septic shock.
   D. The use of this non-formulary drug would be a poor choice and likely lead to patient harm if used.

C. Evaluation of CPS
  1. Continuous QI should include quality indicators and periodic reviews of pharmacist-written documentation and consultations.
  2. These reporting systems allow for collecting, aggregating, and benchmarking data against data from other hospitals and bed size. They increase the credibility of data collection methods and results when evaluated by health care administrators (Appendix 2).
  3. To document raw drug cost savings from changing to less expensive medications, the following method may be applied: subtract the cost of the originally prescribed drug therapy (drug daily cost multiplied by the number of days prescribed) from the cost of the less expensive drug therapy (drug daily cost multiplied by the number of days prescribed). Using this method, the cost of intravenous diluents and admixture fluids and syringes used in the preparation process may be included. Medication costs can also be affected by factors such as shortages and FDA granting using a New Drug Application.
  4. Value of pharmacist interventions should be determined as well. Value may be assigned utilizing cost-avoidance associated with types of pharmacist interventions or with the Overhage and Lukes scale.
  5. Documentation of interventions for reporting to other hospital committees such as the P&T committee should include the following:
     a. Date, time
     b. Type of intervention
     c. Drug(s) involved
     d. Prescriber name, service, and type of health care provider
     e. Duration of time spent completing the intervention
     f. Whether the intervention was accepted or denied, or clarification was achieved
     g. Value of the intervention (e.g. cost avoidance, Overhage & Lukes scale)
  6. Documentation of services should show diversity, effectiveness, cost, and outcomes of activities.
     a. Policy development
     b. Research
     c. Resource use
     d. Management
     e. Leadership
     f. Education
     g. Health care professionals (e.g., physicians, nurses, respiratory therapists)
        i. Pharmacy students
        ii. Pharmacy residents (PGY1, PGY2) and pharmacy fellows
        iii. Pharmacy personnel
  7. Outcomes of documentation
     a. Generate a business plan to expand clinical services:
        i. Background and description
        ii. Market and competitor analysis
        iii. Operational structure and processes
        iv. Financial projections
        v. Milestones, schedules, and action plan
        vi. References
        vii. Supportive documents
        viii. Financial pro forma statements
        ix. Letters of support
     b. Establish additional clinical services.
     c. Expand roles of existing services.
     d. Assess new processes or practices (prescriber privileges or provider reimbursement).

   e. Provide data for QA or research initiatives.
   f. Accreditation purposes
   g. Promotional reasons
   h. Financial impact can be analyzed and used to justify time spent in that area.
8. Reports
   a. Statistical interpretations of services
   b. Satisfaction surveys of their services
   c. Risk reduction
   d. Peer review
   e. Publication
   f. Return on investment data
   g. Future initiatives
9. Pharmacotherapeutic intervention data should be presented and emphasized at as many committee opportunities as possible – this increases the visibility and corroborates the importance of the pharmacy department and the critical care pharmacy services. Box 2 lists examples of pharmacotherapeutic interventions that can be reported. Pharmacotherapeutic intervention data should be presented to the following:
   a. ICU committee
      i. Subcommittees of P&T including ICU, neurology, pediatrics, anticoagulation, or other subspecialty committees.
   b. P&T committee
   c. QA committee
   d. Medication use review committee
   e. Formulary committee
   f. Medication safety committee
   g. Antimicrobial stewardship committee
   h. Medical executive committee – Engages with potential expansion of pharmacy services or cost avoidance
10. Select a regular cadence for which pharmacotherapeutic intervention data will be presented, such as monthly or quarterly (Figure 2). These data should include the type of intervention (Figure 3) and both the raw drug cost savings derived from changing to less expensive drugs and the outcome cost savings such as preventing an adverse event and decreasing the LOS (Figure 4).

Box 2. Examples of Pharmacotherapeutic Interventions

1. Discontinue drug
2. Switch drug
3. Switch drug for less expensive but equally safe and effective drug
4. Drug dosing
5. Drug dosage form
6. Drug route
7. Pharmacokinetic consultation
8. Pharmacotherapy consultation
9. IV-to-PO switch therapy
10. Contraindication
11. Duplicate therapy
12. Nonformulary switch to formulary
13. Nonformulary approval
14. Drug unavailable
15. IV drug incompatibility
16. Drug-drug interaction
17. Drug-food interaction
18. Drug-laboratory test interaction
19. Pharmacogenomics interaction
20. Therapeutic interchange
21. Allergy prevention
22. Medication reconciliation
23. Transfer medication reconciliation
24. Discharge medication reconciliation
25. Discharge counseling
26. Written patient education provided
27. Patient adherence to medications
28. Adverse drug reaction
29. Overdosage
30. Subtherapeutic dose
31. Medication error identification and avoidance
32. Monitoring for efficacy
33. Monitoring for toxicity
34. Ordering laboratory tests for monitoring drug efficacy and toxicity
35. Clarification of medication order
36. Untreated indication
37. Failure to receive medication
38. Immunization recommendation
39. Immunization administered
40. Health risk assessment
41. Rapid response interventions
42. Code interventions
43. CDTM interventions

CDTM = collaborative drug therapy management.

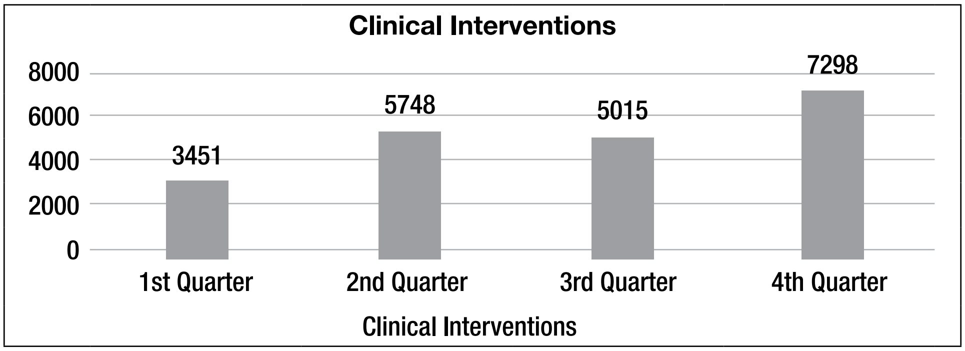


Figure 2. Clinical interventions.

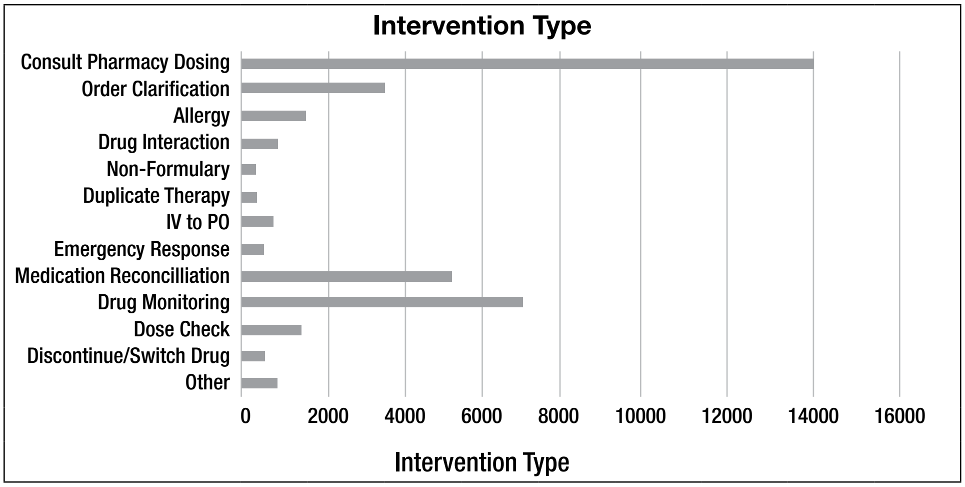


Figure 3. Pharmacotherapy intervention types.

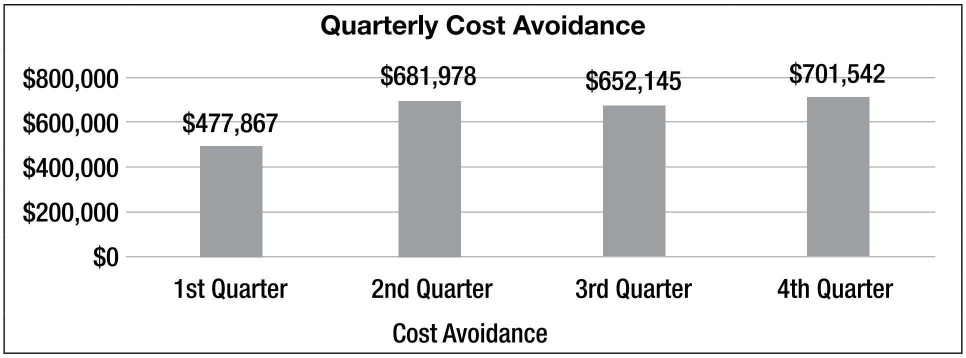


Figure 4. Cost avoidance by quarter.

11. Benchmarking is important in annualizing the total number of pharmacotherapeutic interventions with previous years (Figure 5) and the cost savings with previous years (Figure 6) and in providing rational explanations for any discrepancies noted.

12. Change in the number of interventions and/or potential cost savings should be evaluated cautiously. Changes in number of pharmacists, implementation of guidelines/protocols to standardize care, etc., may impact these numbers and should be considered when assessing.

13. Pharmacotherapeutic interventions that are reported may be prioritized according to their clinical impact on patient safety and cost savings. Examples of high-priority pharmacotherapeutic interventions that should be reported include the following:
    1. Allergy prevented
    2. Contraindication prevented
    3. Drug dosing adjustments
    4. Duplicate therapy avoided
    5. Drug interactions avoided
    6. Medication reconciliation intervention
    7. Ordering laboratory tests for monitoring of drug safety and efficacy
    8. Switching drug for less expensive but equally safe and effective drug

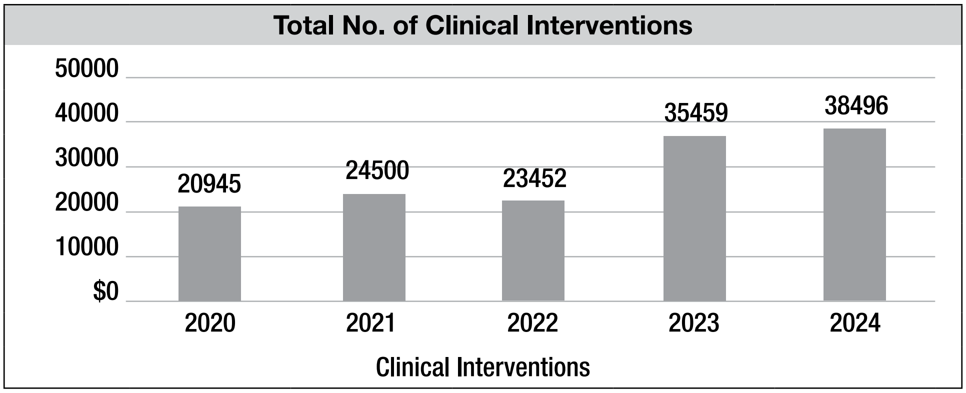


Figure 5. Annual pharmacotherapy interventions 2020–2024.

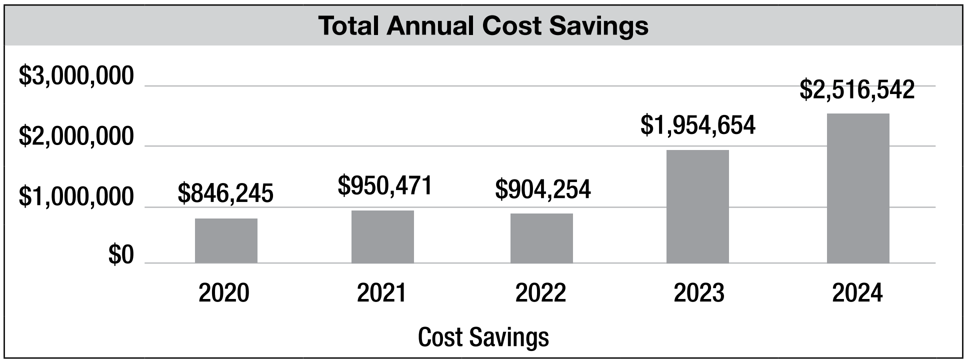


Figure 6. Annual raw drug and outcome cost savings 2020–2024.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

Using evidence-based practice helps provide support in creating a clinical pathway with support and agreement among practitioners (Answer B is correct). Using closed-loop technology is important when implementing a clinical pathway, as is establishing a physician champion (Answer A). Developing a clinical protocol and pathway comes after the evidence is evaluated (Answer C). Formulary proposals are not a primary factor in implementing a clinical pathway (Answer D).

2. **Answer: C**

A gap analysis compares best practice and current state to identify opportunities for improvement (Answer C is correct). Creating a table of the ISMP best practice recommendations regarding storage and handling of NMBs and comparing them with current practice would be the best way to identify opportunity to improve. A survey could be helpful to learn what other institutions are doing, but it does not ensure they are in line with best practices. It could provide additional information but would not show where gaps exist in current state and best practice at your institution (Answer A is incorrect). Answer B is incorrect because it is jumping right to solutions without completing the gap analysis. Answer D is also incorrect because surveying the staff would not provide information on the best practice gaps that exist.

3. **Answer: B**

Answer A is incorrect because the patient name and dose do not need to be on the label per the NPSG requirements. Both drug name and expiration date/time should be. Answer B is correct because all of these must be on the label of a medication drawn up in the perioperative setting. Answer C is incorrect because the patient name and drug dose are not needed on the label but drug name and concentration do. Answer D is incorrect because drug dose does not need to be on the label.

4. **Answer: B**

Current data show that the critical care pharmacist affects many areas associated with TJC measures. According to TJC's current measures, the critical care pharmacist affects procoagulant reversal agent initiation for ICH (Answer B is correct). The ED median time from ED arrival to ED departure for admitted ED patients is not affected by the pharmacist (Answer A is incorrect). Hemorrhage transformation for patients treated with intravenous alteplase therapy or mechanical endovascular reperfusion therapy is also not affected by the pharmacist (Answer C is incorrect). Although the pharmacist would have impact on the severe sepsis and septic shock management bundle, this is not currently a required measurement (Answer D is incorrect).

5. **Answer: A**

Defining the problem is the first step in LEAN (Answer A is correct). The LEAN strategy involves attempting to remove the team members' opinions so their emotions do not influence the process. Hence, asking the nurses their opinion for the spike in catheter-related bloodstream infections influences their emotions (Answer B is incorrect). Identifying operational barriers is a LEAN process, however a transportation barrier is not related to catheter related blood stream infections (Answer C is incorrect). Describing the past process is not a LEAN evaluation component (Answer D is incorrect).

6. **Answer: C**

An MUE is drug- or disease-specific and is best suited for reviewing vancomycin dosing and the ordering of vancomycin blood concentrations (Answer C is correct). Quality assurance surveys are best suited for monitoring the medication use process that may not be specific to a drug or disease, such as the review of a pharmacist's notes in the EHR, review of the accuracy of expiration dates placed on intravenous admixture products, and review of the frequency of drug interaction warnings on the CPOE system (Answers A, B, and D are incorrect).

7. **Answer: A**

Justification to hospital leadership should provide financial benefit to the organization as well as improvement in patient outcomes and safety. Antibiotic stewardship outcomes as well as cost savings would provide both of these above and help justify additional pharmacy FTEs (Answer A is correct). Although provider education and in-services can be of benefit, it is difficult to justify these with cost savings or outcome benefits (Answer B is incorrect). Although many clinical pharmacists spend time on rounds, this time is not value added without interventions and cost savings metrics associated with it (Answer c is incorrect). While renal dose adjustments and intravenous to oral conversion are interventions clinical pharmacists frequently make, they do not provide measurable metrics unless associated with a cost savings and safety benefit (Answer D is incorrect).

8. **Answer: C**

Answer A is incorrect because it solely focuses on cost with little rationale on how this might impact the patient clinically. Answer B is incorrect because it is worded such that it is implying harm will result if the provider does not take the recommendation. Answer C is correct because it is worded that the provider should consider the recommendation as well as the rationale as to why. Answer D is incorrect because it is focusing on the fact that it is non-formulary and would likely cause harm if the provider does not take the recommendation.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: D**

Financial justification for a critical care pharmacist has been shown by the impact of clinical pharmacists on critically ill patients. The critical care pharmacist can reduce adverse events in the critically ill population, reduce order prescribing errors, optimize the correct drug for the correct disease process, decrease the LOS, reduce medication administration errors, and reduce inappropriate antibiotic use. One of the main financial impacts on critically ill patients is antimicrobial therapy. Using an anticoagulation reversal stewardship program will most affect the institution (Answer D is correct). Developing protocols is important in streamlining practice in the critically ill population and can reduce health care costs, and prescribing errors and medication administration errors can result in adverse events to the patient, but none of these would have the most significant effect on finances (Answers A, B, and C are incorrect).

2. **Answer: B**

Practice environment constraints include financial disincentives (not enough staff to support delirium screening), organizational constraints (screening process takes up valuable nursing time), perception of liability (if the screen is conducted and the test is positive, the provider will be blamed), and patient expectations (Answer B is correct). Another barrier to implementing delirium screening includes the key stakeholders' standard or routine work of the process, which is based on opinion, not evidence (Answer A is incorrect). A third barrier involves the professional context and includes clinical uncertainty. Practitioners may believe they have adequate skills to act. In addition, information overload occurs with the vast amount of literature being published. An example of a knowledge barrier includes providers being unfamiliar with how to perform delirium screening (Answer C is incorrect). A fourth barrier is when the key stakeholders' opinion does not agree with screening patients for delirium because of changes in evidence-based medicine and possible knowledge gaps (Answer D is incorrect).

3. **Answer: A**

Evaluating the use of pharmacotherapy in SUP in the ICU is best suited for an MUE (Answer A is correct). The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes—in this case, pharmacotherapy in SUP. Although one component of an MUE is PI, a review of the quality should occur before determining whether a PI project is necessary (Answer B is incorrect). An interventional MUE incorporates a review of quality in the form of making a pharmacotherapeutic intervention—PI. Although reviewing ADE data and medication error data from the ICU is helpful in detecting and determining problems associated with the use of pharmacotherapy in SUP, these are isolated events and are reporter-dependent, and a lack of reports does not ensure that the use of pharmacotherapy in SUP is appropriate (Answers C and D are incorrect). Only an MUE is a robust and comprehensive method of evaluating the use of pharmacotherapy in SUP.

4. **Answer: B**

Evaluating the management of warfarin-induced hypoprothrombinemia is best suited for an MUE. The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes; an MUE is drug-, drug class–, or disease-specific—in this case, management of warfarin-induced hypoprothrombinemia (Answer B is correct). Quality assurance is a process for monitoring the effectiveness and safety of the medication use process that includes prescribing, dispensing, and administering medications. Evaluating pharmacist verification times for routine orders in the ICU, drug interaction warnings on the CPOE system, and duplicate warnings on the CPOE system is not necessarily drug- or disease state–specific and is best suited for a QA review (Answers A, C, and D are incorrect).

5. **Answer: A**

The next best step is determining which patients with cardiac arrest should receive targeted temperature management. (Answer A is correct). Best practices have already been identified, so additional literature evaluation is not needed. (Answer B is incorrect). Finally, data will be collected on the current process of managing targeted temperature management (Answer D is incorrect), which will be evaluated to determine the areas for improvement in the outcome desired. The current process has already been determined, as provided in the question (Answer C is incorrect).

6. **Answer: D**

Because the data have already been collected, they must be analyzed to determine the baseline time to antibiotics (Answer D is correct). The measuring phase includes collecting the data, which has already been completed (Answer A is incorrect). Establishing methods is part of the design (Answer B is incorrect). The change process being implemented is the improvement phase (Answer C is incorrect).

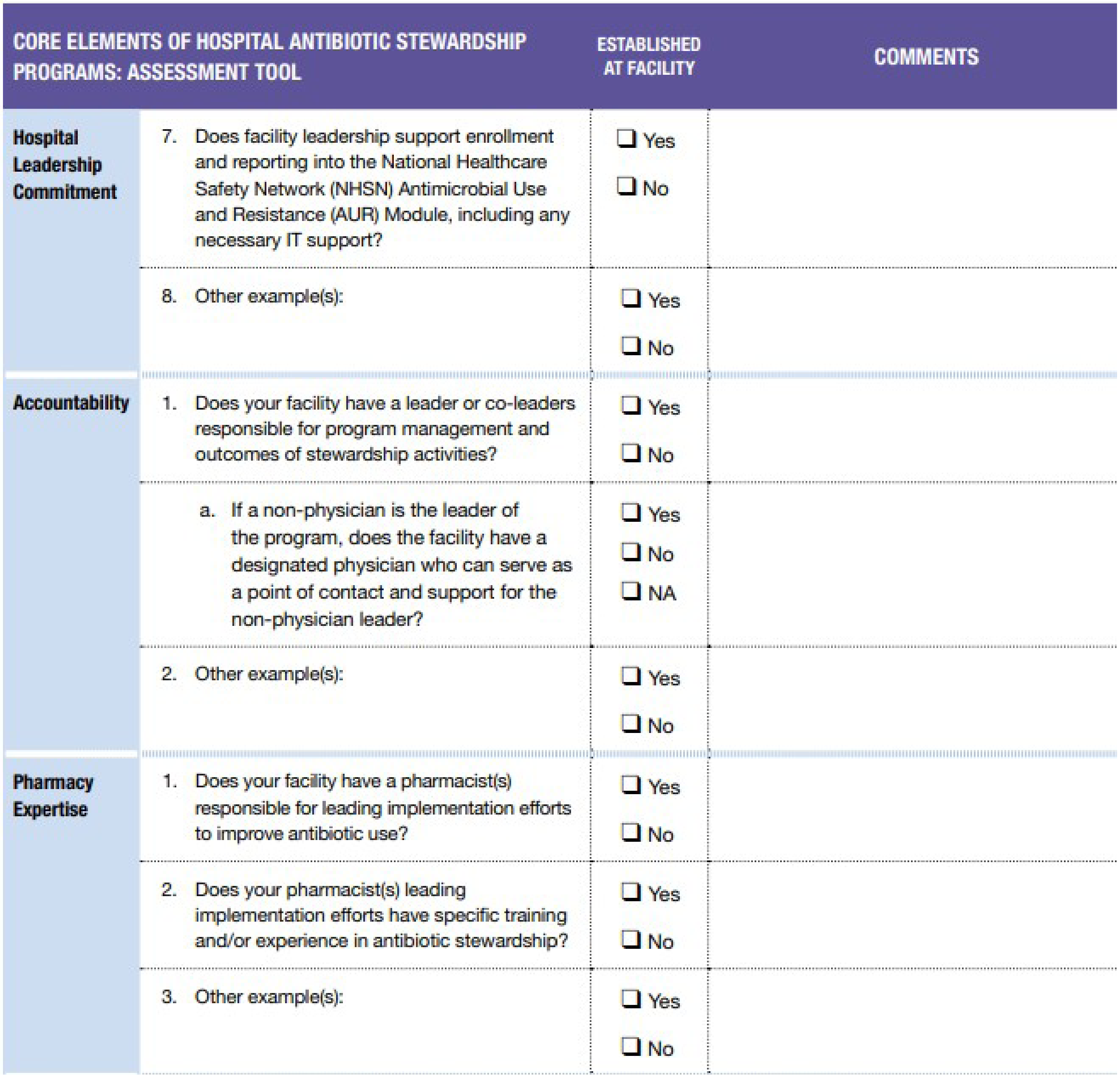
7. **Answer: A**

Using weighted metrics for each critical care pharmacist activity – quantified over time and annualized – more accurately quantifies a critical care pharmacist's activities (Answer A is correct). The number of cardiac arrest codes attended each month, number and severity of hospital-acquired *Clostridioides difficile* infections each year, and the number of in-services provided each year are important, but do not quantify a comprehensive list of a critical care pharmacist's activities individually (Answers B, C, and D are incorrect).

8. **Answer: A**

Sepsis management bundle and VTE prophylaxis are quality measures reported to CMS (Answer A is correct). Thrombolytic therapy for patients with stroke is correct, but stress ulcer prophylaxis is not reported (Answer B is incorrect). Heart failure readmissions are reported, but pneumonia vaccination rates are not (Answer C is incorrect). Use of ventilator bundles is not reported, but rates of acute coronary syndrome readmission are reported (Answer D is incorrect).

Appendix 1. Centers for Disease Control and Prevention (CDC) – The Core Elements of Hospital Antibiotic Stewardship Programs: Antibiotic Stewardship Program Assessment Tool (excerpt)



CORE ELEMENTS OF HOSPITAL ANTIBIOTIC STEWARDSHIP PROGRAMS: ASSESSMENT TOOL		ESTABLISHED AT FACILITY	COMMENTS
Hospital Leadership Commitment	7. Does facility leadership support enrollment and reporting into the National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module, including any necessary IT support?	☐ Yes ☐ No	
	8. Other example(s):	☐ Yes ☐ No	
Accountability	1. Does your facility have a leader or co-leaders responsible for program management and outcomes of stewardship activities?	☐ Yes ☐ No	
	a. If a non-physician is the leader of the program, does the facility have a designated physician who can serve as a point of contact and support for the non-physician leader?	☐ Yes ☐ No ☐ NA	
	2. Other example(s):	☐ Yes ☐ No	
Pharmacy Expertise	1. Does your facility have a pharmacist(s) responsible for leading implementation efforts to improve antibiotic use?	☐ Yes ☐ No	
	2. Does your pharmacist(s) leading implementation efforts have specific training and/or experience in antibiotic stewardship?	☐ Yes ☐ No	
	3. Other example(s):	☐ Yes ☐ No	

Exert from Source: Centers for Disease Control and Prevention (CDC). The Core Elements of Hospital Antibiotic Stewardship Programs: Antibiotic Stewardship Program Assessment Tool. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. Available at the following website at no charge. https://www.cdc.gov/antibiotic-use/healthcare/pdfs/assessment-tool-P.pdf.

Appendix 2. Example of Interventions and Clinical Pharmacy Services Cost Savings

Pharmacy Department
Data for 2024

Measure	Benchmark	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Pharmacotherapeutic interventions	None	7398	8748	9015	10,298
Outcomes cost and raw drug cost savings from pharmacotherapeutic interventions	None	$477,867	$681,967	$652,145	$701,542

Findings/Conclusion: For 2021, the total number of pharmacotherapeutic interventions remained the same from the previous year with 20,940 interventions, realizing $846,245 in outcomes and raw drug cost savings. For 2022, the total number of pharmacotherapeutic interventions remained similar to the prior year with 24,500 interventions, realizing $950,471 in outcomes and medication use savings. For 2023, the total number of pharmacotherapeutic interventions remained similar to the prior year with 23,452 interventions, realizing $904,254 in outcomes and raw drug cost savings. For 2024, the total number of pharmacotherapeutic interventions increased with 35,459 interventions documented, realizing $2,513,521 in outcomes and raw drug cost savings.

Pharmacotherapeutic interventions performed by clinical pharmacists consist of making downward and upward dosing adjustments of medications, providing pharmacokinetic consultations, avoiding drug-drug and drug-food interactions, avoiding toxic medications, avoiding drug-disease contraindications, avoiding drug-allergy interactions, approving and dosing restricted antibiotics, switching patients from intravenous medications to oral medications, initiating more effective or safer drug therapies, initiating equally efficacious but less expensive medications, discontinuing unnecessary and duplicate medications, changing dosage forms according to patient tolerance, switching nonformulary to formulary medications, and making recommendations to monitor for efficacy and toxicity.

Clinical pharmacists review and respond to abnormal drug blood concentration assays and laboratory values such as serum chemistry and coagulation profiles as they pertain to medication management. Notes documenting the interventions are placed in the pharmacy profile. Depending on the quantity of pharmacotherapeutic interventions and the resulting cost savings, the Pharmacy Department's efforts to document clinical interventions, ensure medication safety, and contain medication-related costs have been very effective.

Action Indicated: No additional actions are required. The Pharmacy Department will continue to perform and document clinical interventions and evaluate the resulting cost savings.

PHARMACOECONOMICS AND SAFE MEDICATION USE

ADRIAN WONG, PHARM.D., MPH, FCCP, FCCM, BCCCP

BETH ISRAEL DEACONESS MEDICAL CENTER
BOSTON, MASSACHUSETTS

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Learning Objectives

1. Apply the principles of pharmacoeconomics to patient care.
2. Differentiate between a medication error, an adverse drug event (ADE), a preventable ADE, and an adverse drug reaction (ADR).
3. Design an ADE reporting program, including committee structure, committee reporting mechanisms, and methods of detecting, reporting, and managing ADEs.
4. Provide recommendations for improving medication use safety using the 2017 SCCM Safe Medication Use Guidelines for the ICU.
5. Provide safety measures for drug interaction detection and prevention.
6. Develop a drug formulary proposal.

Abbreviations in This Chapter

ADE	Adverse drug event
ADR	Adverse drug reaction
CDS	Clinical decision support
EHR	Electronic health record
P&T	Pharmacy and therapeutics (committee)
QALY	Quality-adjusted life-year

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.
Your institution wants to evaluate the addition of coagulation factor Xa (recombinant), inactivated-zhzo to your formulary for reversal of direct oral anticoagulants.

1. Which best describes the type of cost this medication would have?
   A. Fixed medical.
   B. Variable medical.
   C. Indirect.
   D. Incremental.

2. Your institution wants to use pharmacoeconomic data to evaluate the impact of this medication on neurologic disability and cost compared with prothrombin complex concentrate. Which analysis would be best to find in the literature?
   A. Cost-benefit.
   B. Cost-effectiveness.
   C. Cost-minimization.
   D. Cost-utility.

3. A 60-year-old patient is admitted to the surgical ICU with a documented history of cefuroxime allergy (shortness of breath). The patient is administered ceftriaxone and develops a life-threatening anaphylactic reaction. Which best describes this patient's reaction to ceftriaxone?
   A. Adverse drug reaction (ADR).
   B. Side effect.
   C. Adverse drug event (ADE).
   D. Preventable ADE.

4. A 50-year-old patient is admitted to the neurology ICU from the medical floor for the management of an apixaban-induced cerebral hemorrhage. Which medication would best have been used as an effective tracer medication to help detect this ADE?
   A. Coagulation factor VIIa.
   B. Phytonadione.
   C. Protamine.
   D. Prothrombin complex concentrate.

Questions 5 and 6 pertain to the following case.
As a new pharmacist in the medical ICU at your institution, you have been tasked with improving the safety of medication use in the ICU. You have read the 2017 SCCM Guidelines for Safe Medication Use in the ICU and are prepared to provide recommendations to the interdisciplinary critical care committee regarding your suggestions.

5. According to the grading system of the guideline recommendations, which is the best initial recommendation to improve medication use safety, given the strength of recommendation?
   A. Fully integrating the institution's electronic health record (EHR) systems to improve communication.

B. Integrating interruptive clinical decision support (CDS) into the EHR.
C. Creating a policy requiring that intravenous medications can only be prepared by pharmacists.
D. Investing in smart intravenous infusion pumps to reduce medication errors.

6. After your institution has integrated your recommendation into routine medical care, a former patient recommends including the patient and other caregivers in reducing medication errors. According to the available literature, which best supports this recommendation?

A. The 2017 SCCM guidelines provide a strong recommendation for this integration into routine care.
B. Areas in the hospital outside the ICU provide data supporting this integration.
C. Data analyses on direct observations of interactions between the medical team and patients have shown a reduction in medical errors in the ICU.
D. Data analyses on chart reviews of ICU patients have shown that these reported outcomes are not routinely accounted for.

7. A 50-year-old patient was initiated on meropenem for empiric coverage of pneumonia, given prior culture data. They were subsequently initiated on valproic acid for the management of agitation; however, this was not effective for management and resulted in self-extubation and subsequent reintubation. In investigating this adverse event, which method would best evaluate the likelihood of its occurrence?

A. Drug interaction database.
B. Drug interaction probability scale.
C. Naranjo nomogram.
D. Roussel Uclaf Causality Assessment Method (RUCAM).

8. Your hospital wants to add meropenem/vaborbactam, a broad-spectrum antimicrobial targeting highly drug-resistant organisms that is FDA approved for complicated UTIs, to the formulary. Which would be the most appropriate restriction to its use?

A. Restriction to intensivist use.
B. Restriction to patients with hospital-acquired pneumonia.
C. Restriction to infectious diseases clinicians' approval.
D. Restriction to patients with appropriate cardiac monitoring.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 5–7
    b. Task C: 2, 4, 5
2. Domain 3: Professional Practice
    a. Task A: 1-6
    b. Task B: 1

I. PHARMACOECONOMICS

A. Overview
  1. Pharmacoeconomics is the description and analysis of the costs of drugs and pharmaceutical services as well as their effects on individuals, health care systems, and/or society.
  2. Economic evaluations identify, measure, and compare the costs and consequences of a pharmaceutical product or service. These can convey different results, depending on disease state/therapy being evaluated, alternative therapies, perspective (e.g., payer, provider, patient, society), and intended outcome.
    a. Full pharmacoeconomic analyses include the following:
      i. Cost-benefit
      ii. Cost-effectiveness
      iii. Cost-minimization
      iv. Cost-utility
    b. Humanistic outcomes or patient-reported outcome measures include the following:
      i. Functional status
      ii. Health status
      iii. Health-related quality of life
      iv. Patient satisfaction
      v. Quality of life

B. Types of Costs
  1. Costs versus charges
    a. Although the term *charges* alone is often used in the literature, *charges* are actually costs (also termed *expenses*) plus profit or a combination of the acquisition cost for a specific item used (e.g., cost of medication dose administered) plus *estimated* costs to provide the service (e.g., workflow and personnel associated with the process for medication use) plus a *markup*.
  2. Types of cost (Table 1)

Table 1. Summary of Types of Cost Used in Economic Evaluations

Type of Cost	Definition	Examples
Direct • Medical	Costs associated with prevention, detection, or treatment of a disease or illness Costs associated with medical care	**Fixed** (costs that remain constant and are not dependent on volume of use; not typically included in pharmacoeconomic evaluations): Rent, salaried workers **Variable** (costs depend on volume of use): Laboratory tests, medications, procedures
• Non-medical	Costs as a result of disease or illness that do not involve the purchase of medical services	Child care, specialty diets, transportation
Indirect	Costs associated with morbidity or mortality, related to change in productivity as a result of disease or illness	Costs because of inability to work, income lost because of premature death
Intangible	Costs associated with nonfinancial outcomes of disease	Costs from posttraumatic stress disorder from ICU survival; post-ICU syndrome
Incremental	Additional costs to purchase additional benefit or effect of medical care	Additional medications to control atrial fibrillation that started in ICU
Total	Inclusion of all the above costs	N/A

N/A = not applicable.

C. Types of Pharmacoeconomic Evaluations (Table 2)
  1. There are several types of full economic evaluation. The main difference between the types of full economic evaluation is how the benefits to the individual are measured and valued.
  2. Cost analysis
     a. Compares only cost (i.e., no effectiveness) of two or more treatments or services
     b. Potentially more applicable than cost-minimization analysis when effectiveness is not known
  3. Cost-benefit analysis
     a. Systematic approach assessing strengths and weaknesses of treatments or programs to determine the best approach to attaining benefits while minimizing expense
     b. Both costs and outcomes are measured in monetary units, including direct and indirect benefits, allowing for a direct comparison.
     c. Identifies yield of investment (e.g., justification of post-ICU clinic, comparison of a pharmacokinetics service with a vaccination program)
     d. Results may be expressed with cost-benefit ratio, net cost, or net benefit.
  4. Cost-effectiveness analysis
     a. Compares two or more treatment alternatives or programs in which resources (e.g., treatments, services) are used
     b. Costs are measured in monetary terms, whereas outcomes are measured in units of effectiveness.
     c. Determines which alternative can produce the desired effect or maximization of effect, which may by a more expensive option that provides a more desirable outcome than a less expensive option
     d. Results are expressed as the incremental cost-effectiveness ratio (ICER), which is defined as the additional cost to the next most effective intervention producing another unit of output. These results can be displayed in a cost-effectiveness plane, which graphs the ICER in four quadrants (x-axis is effectiveness; y-axis is cost).
  5. Cost-minimization analysis
     a. Compares two or more treatment alternatives or programs for which the outcomes are virtually identical (e.g., effectiveness) except for costs; therefore, results are expressed in monetary form, which allows for ease in examining resource outcomes
     b. Costs are compared to determine the least expensive alternative with a noninferior efficacy.
     c. Should not be used if no evidence supports the therapeutic equivalence of the treatment alternative
  6. Cost-utility analysis
     a. Comparison of two or more treatment alternatives or programs in which costs are measured in monetary terms and outcome is expressed with respect to patient preferences, quality of life, or quality-adjusted life-years (QALYs)
        i. Form of cost-effectiveness analysis in which values (utilities) are assigned to the outcome
        ii. Life and death are reference states for the utilities, with perfect health = 1.0 and death = 0.0 (although to a patient, a certain state [e.g., vegetative] may be worse than death, allowing for a negative utility).
        iii. Utilities or a patient's preference for a disease state can be measured by obtaining information from the literature, approaching a convenience sample of experts, using decision theory with a direct approach, or using psychometric methods with indirect approaches.
           (a) Direct approaches include rating scales, time trade-off (acute and chronic conditions), and standard gamble (acute and chronic conditions).
           (b) Indirect approaches include multi-attribute health state scores (e.g., quality-of-life assessment tools).
     b. To calculate QALYs, the life-years gained is determined and then multiplied by the utility of that life-year. For example, if persons have a life expectancy of 20 years but have a disability and believe they are functioning at only 70% of their capacity, the QALY is 20 years × 0.7 = 14 QALYs.
     c. Measures the function and overall well-being of patients using quality-of-life assessment tools, such as those used in the ICU, which are general and/or disease-specific (e.g., EuroQol 5D Questionnaire, European Organization for Research and Treatment of Cancer 8 Dimensions)

Table 2. Summary of Pharmacoeconomic Evaluations[a]

Economic Evaluation	Cost Measurement	Consequences or Outcomes	Measurement/Valuation of Consequence or Outcomes	Example	Challenges
Cost analysis (partial evaluation)	Monetary	Not considered, so not a full economic evaluation	Not considered, so not a full economic evaluation	Cost of cisatracurium compared with rocuronium in patients with acute respiratory distress syndrome (disregarding any outcome)	Challenges limited compared with CMA, CBA, CEA, CUA
Cost-benefit analysis (CBA)	Monetary for total cost of care	Single or multiple effect/outcome that does not have to be common to both alternatives Effects are translated to monetary units, so comparison among various alternatives is possible	Monetary units	Comparison of pharmacist-led blood factor prescription with standard of care on andexanet costs to hospital	Translating consequences to monetary units
Cost-effectiveness analysis (CEA)	Monetary for total cost of care	Must have a single effect/outcome of interest for all alternatives considered, and the effect/outcome is achieved to a different degree The outcomes of the alternative strategies are not equivalent and are measured in unidirectional natural units	Nonmonetary physical units of effectiveness. (e.g., life-years gained, surrogate end point)	Comparison of andexanet with 4F-PCC on bleeding-related mortality	Determining the probabilities of the clinical pathway for the decision tree to determine the consequences
Cost-minimization analysis (CMA)	Monetary for total cost of care	Must be evaluated Single effect/outcome of interest for all alternatives that were shown to be equivalent	Identical	Comparison of medication and its biosimilar on cost because equivalent outcomes are assumed	Proving consequences are identical
Cost-utility analysis (CUA)	Monetary for total cost of care	Single or multiple effect/outcome that does not have to be common to both alternatives Effects are translated to QALYs, so comparison among various alternatives is possible	Utility values and QALYs	Comparison of andexanet with 4F-PCC on patient outcomes, measured by patient utility (QALY)	Measuring utilities

[a] Andexanet = coagulation factor Xa (recombinant), inactivated-zhzo.

4F-PCC = 4-factor prothrombin complex concentrate; QALY = quality-adjusted life-year.

Modified from: Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes, 4th ed. Oxford University Press, 2015.

D. Application of Pharmacoeconomics
   1. Formulary management to determine whether newly marketed or approved medications should be included/excluded with/without use criteria that may affect prescribing patterns
      a. Creation of therapeutic interchanges for various drug classes or individual agents (ie, biosimilars) with known equivalence
   2. Development of clinical guidelines, policies, or protocols to promote the most cost-effective and desirable use of medications in the context of safety and efficacy
      a. One situation in which this may be forced is a drug shortage that affects the availability of standard of care at your institution. This forced evaluation may identify more cost-effective practices based on evidence-based medicine.
   3. Implementation of drug use policy to promote the most efficient use of health care products and services
   4. Perform program evaluations to determine the value of an existing medical or pharmacy service or the potential worth of starting a new service, in addition to guiding the establishment of key business objectives or metrics of growth, adoption, or process control
   5. Population health analytics (e.g., use of pharmacoeconomic analyses to determine evidence-based medicine treatment decisions within a health system)
   6. Determine individual patient treatment decisions
   7. Publication of pharmacoeconomic evaluations with pharmacist involvement

Patient Case

1. A 30-year-old patient is admitted to the surgical ICU after a motor vehicle accident. Which would best exemplify an indirect cost from their perspective?
   A. Loss of wages from occupation as an engineer.
   B. Effects of posttraumatic stress disorder from the accident.
   C. Fentanyl administered to manage pain.
   D. Cost of the ambulance that transported them to the hospital.

II. DRUG-RELATED EVENTS: MEDICATION ERRORS, ADES AND ADRS, PREVENTABLE ADES

A. Overview
   1. In the United States, 770,000 injuries or deaths are caused by ADRs annually; the cost burden of ADEs is greater than $5.6 million per hospital.
      a. ADEs are estimated to occur in up to 7% of hospital admissions, with up to 14% of hospital admissions attributable to ADEs.
      b. A severe ADE increases the hospital length of stay by 8–12 days at a cost of $16,000–$24,000 per patient.
      c. The cost burden of preventable ADEs in the United States is $4.1 million per hospital annually. Medical malpractice lawsuits are often related to, or occur because of, ADEs.
   2. The risk of ADEs increases when patients are critically ill because of a higher chance of being administered a high-risk medication and the potential for altered response to medications because of altered pharmacokinetics and organ failure.

3. The Joint Commission medication management standard requires hospitals to respond to actual or potential ADEs, significant ADRs, and medication errors. At the very least, hospitals need to respond, document and report, and manage ADEs. The pharmacist, who is the drug expert, should play an integral role in prospective order verification to prevent ADEs by intervening as needed.

B. Definitions of Drug-Related Events

1. Figure 1 summarizes drug-related events.

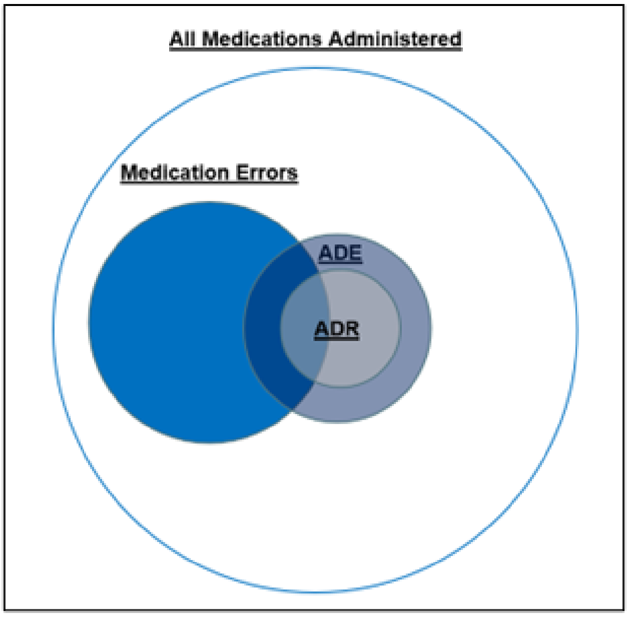

Figure 1. Types of drug-related events.

This figure details types of drug-related events including medication errors, adverse drug events (ADEs), and adverse drug reactions (ADRs). The largest circle illustrates all medications administered, with the next largest circle indicating which medications administered were associated with a medication error that reached the patient. The third largest circle illustrates ADEs, which may be a result of medication errors (i.e., overlap between circles). ADEs that are a result of medication errors are therefore preventable. The smallest circle illustrates ADRs, which are a type of ADE that causes patient harm/injury. Some of these are the result of medication errors, as suggested by the overlap between the "Medication Errors" and "ADR" circles.

2. Medication errors
   a. Mishaps that occur during the medication use process (e.g., reconciling, prescribing/ordering, transcribing, dispensing, administering, monitoring)
      i. Medication errors that are intercepted and stopped before they occur are called "near misses."
      ii. Some medication errors cause harm (result in an ADE), and some do not. Medication errors should be reported through the health system's patient incident reporting system. Harm is physical or psychologic injury or damage to a patient's health, including both temporary and permanent injury.
   b. Medications errors can be categorized as the following:
      i. Category A: No error – Scenarios that can cause error
      ii. Category B: An error occurred but did not reach the patient
      iii. Category C: An error occurred and reached the patient but did not cause harm
      iv. Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient or required intervention to prevent harm
      v. Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention

        - vi. Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization
        - vii. Category G: An error occurred that may have contributed to or resulted in permanent patient harm
        - viii. Category H: An error occurred that required intervention necessary to sustain life
        - ix. Category I: An error occurred that may have contributed to or resulted in the patient's death
    - c. Medication errors are defined by The Joint Commission as a sentinel event that includes events such as those that cause severe temporary harm (requiring intervention), permanent harm, or death (e.g., potentially category E, categories F–I).
    - d. May be reported through the Institute for Safe Medication Practices (ISMP Medication Error Reporting Program)
        - i. A confidential and voluntary system, investigated by ISMP staff and then reported to the FDA's MedWatch program and product vendors
        - ii. A separate reporting method is used for vaccines, specifically the ISMP Vaccine Errors Reporting Program. Vaccine medication error reports provide an option to submit the vaccine's manufacturer name, dosage, lot number, expiration date, and National Drug Code.
        - iii. Consumers may also report medication errors through ISMP.
        - iv. Medication errors may be reported directly to the FDA by the MedWatch system. The FDA's MedWatch allows ADE and medication error reporting.
3. Adverse drug events
    - a. *Injuries* resulting from use of a drug, which include harm caused by the drug (ADRs and overdoses) and harm from use of the drug, including dose changes and discontinuations of drug therapy
    - b. Overall, *ADE* is the broader term used to describe any harmful event associated with a medication, including inappropriate use such as an overdose, whereas *ADR* is used when an adverse response, including harm, occurs with normal use of the medication.
4. Preventable ADEs
    - a. A preventable ADE occurs when a breach of standard professional behavior, practice, or technique was identified or when necessary precautions were not taken, or when the event was preventable by modifying behavior, practice, technique, or care.
        - i. Results from any medication error that reaches the patient and causes harm
        - ii. About 30%–50% of all ADEs are preventable.
        - iii. Drug interactions account for 3%–5% of all preventable in-hospital ADRs (drug interactions are discussed further in section IV, Drug Interaction Surveillance and Prevention).
    - b. Examples of preventable ADEs
        - i. Carbamazepine prescribed for an Asian patient with bipolar disorder without testing for the *HLA-B*1502* allele; in turn, the patient develops carbamazepine-induced toxic epidermal necrolysis
        - ii. Heparin administered without the use of weight-based dosing, causing a supratherapeutic partial thromboplastin time and an intracranial hemorrhage
        - iii. Phenytoin mixed accidentally with dextrose rather than normal saline, causing precipitation and lack of drug potency and leading to a patient developing withdrawal seizures and status epilepticus
5. Nonpreventable ADEs
    - a. ADEs not associated with a medication error and are unintended reactions without known mitigation strategies resulting in patient harm (a patient with a bleed despite appropriate dosing, administration, and monitoring of the anticoagulant)

        - i. An example of nonpreventable ADEs would include drug shortages that affect standard of care. The norepinephrine shortage in 2011 was found to be associated with a 15% increased risk of in-hospital mortality.
- 6. Adverse drug reactions
    - a. Definitions
        - i. WHO defines ADRs as "any response to a drug which is noxious and unintended, and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."
        - ii. According to Karch and Lasagna (JAMA 1975;234:1236-41), ADRs are "any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose."
        - iii. The primary difference between the WHO and Karch and Lasagna ADR definitions is that, according to the WHO definition, therapeutic failures are an unintended effect and an ADR, whereas according to the definition by Karch and Lasagna, they are not. Both definitions refer to doses normally used in humans, which exclude overdoses and medication errors that exceed normal doses.
        - iv. ADRs caused by therapeutic failures with easily retrievable, detailed data that document the drug and the therapeutic failure can significantly affect patient care.
    - b. Examples by definition
        - i. WHO
            - (a) Clopidogrel failure to prevent an ischemic stroke
            - (b) Enoxaparin failure to prevent deep vein thrombosis
            - (c) Famotidine failure to prevent intravenous ketorolac-induced gastropathy
            - (d) Pantoprazole failure to prevent GI bleeding from a stress ulcer in a critically ill patient
        - ii. Karch and Lasagna
            - (a) Lorazepam when used to treat anxiety may cause sedation.
                - (1) This is an unintended adverse reaction; conversely, lorazepam for sedation in a critically ill patient is an intended effect, not an ADR.
            - (b) Diphenhydramine causing unintended sedation when used to treat allergic rhinitis
                - (1) This is an ADR; conversely, diphenhydramine as a sedative hypnotic is an intended effect, not an ADR.

C. FDA-Reportable ADEs

- 1. For reporting an ADE to the FDA, the FDA defines ADEs as serious adverse events related to drugs or devices in which "the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage." FDA-reportable serious ADEs may include the following:
    - a. Acetaminophen-induced hepatotoxicity
    - b. Apixaban-induced intracranial hemorrhage
    - c. Gentamicin-induced irreversible ototoxicity
- 2. The FDA is also interested in serious ADE reports for newly marketed drugs or novel adverse events that have not previously been reported for new or old drugs.
    - a. The FDA Adverse Reporting System (FAERS) database is designed as a postmarking surveillance tool for medications and biologics. Other therapies, such as medical devices, have their own reporting system.
    - b. The CDC and FDA co-sponsor the Vaccine Adverse Event Reporting System (VAERS), which is focused on identifying potential signals for adverse events associated with vaccines licensed for use within the United States.

3. The FAERS and VAERS databases are used as postmarketing surveillance systems. Limitations of FAERS and VAERS include the following:
    a. Lack of certainty of adverse event (i.e., may not be validated)
    b. Underreporting
    c. Less severe adverse events likely to be underreported
    d. Potential lack of detail provided
4. Reporting of ADEs by health care professionals and consumers to the FDA is voluntary and may be done through the FDA's MedWatch program (begun in 1993). All of the following may be reported with respect to an FDA-regulated medication, biologic, tobacco product, dietary supplement, cosmetic, or medical device:
    a. Serious ADE
    b. Serious ADR
    c. Product quality problem
    d. Product use error
    e. Therapeutic inequivalence
    f. Therapeutic failure
5. Clinicians may report an ADE directly to the drug's manufacturer. The pharmaceutical manufacturer has a legal responsibility to follow up with the reporter on all ADEs reported and to report the ADE to the FDA.
6. ADE reports and medication error reports submitted directly by health care professionals or manufacturers are entered in the FAERS database.
7. If the FDA detects a safety concern, regulatory action may be needed to protect the public, such as updating the product labeling, restricting the drug, communicating the safety concerns to health care professionals and consumers, or removing the drug from the market.

D. Designing an ADE Reporting Program
1. A comprehensive ADE program should have a policy and procedure, with guidelines for ADE detection, reporting, management, surveillance, and education.
    a. The purpose of a reporting program includes improving patient care, education of health care professionals, complementing organizational risk management with respect to medication use, and assessing safety of medication therapies.
    b. A comprehensive program includes a surveillance system, which includes prospective and retrospective surveillance systems, and tools to improve medication safety, including event monitoring and CDS.
    c. Appendix 1 shows an ADE reporting form.
2. Because of pharmacists' expertise in drug-induced diseases and their role in preventing and managing ADEs, pharmacists often serve as chair or co-chair of the ADE/medication safety committee.
3. The ADE committee should be interdisciplinary and composed of the following:
    a. Prescribers
    b. Pharmacists
    c. Nurses
    d. Risk management personnel
    e. Quality assurance and performance improvement personnel
    f. Other health care providers
    g. Informaticist
    h. Administrator
4. In general, the ADE committee is a subcommittee of the pharmacy and therapeutics (P&T) committee that reports to the P&T committee.

5. The ADE committee should meet monthly, bimonthly, or quarterly, depending on the number of reports and actionable items that need review.
6. ADE data can be reported by a specialty unit or service (e.g., emergency medicine, ICU).
7. ADE data can ensure that appropriate preventive measures are developed for that specialty unit.
   a. A proactive method to reduce the incidence of ADEs is a failure mode and effects analysis (FMEA), which is a proactive, structured method to identify potential failure points within a system that may lead to an ADE.
   b. If an ADE has occurred, performance of a root cause analysis, which is a structured method to determine why an ADE occurred (i.e., retroactive), can help identify methods to prevent the recurrence of the ADE in the future.
8. ADR and ADE data should be reported as mild, moderate, or severe. Many scales are available in the literature. Definitions for each should be established. Box 1 provides an example.

Box 1. Definitions for the Degree of ADR or ADE Severity[a]

1. Mild ADR or ADE: Results in heightened need for patient monitoring with or without a change in vital signs, but no ultimate patient harm, or any adverse event that results in the need for increased laboratory monitoring
2. Moderate ADR or ADE: Results in the need for aggressive intervention with antidotes or increased length of hospital stay (e.g., severe hypotension [e.g., BP < 90/50 mm Hg], bleeding necessitating transfusions)
3. Severe ADR or ADE: Results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage (e.g., irreversible hepatotoxicity or renal failure), or death with probable ADE causality nomogram score

[a] Other ADE severity scales are available.

ADE = adverse drug event; ADR = adverse drug reaction; BP = blood pressure.

9. The ADE committee should
   a. Designate which ADEs are preventable, explain why they are preventable, and determine possible preventive measures
   b. Determine which ADEs will be reported to the FDA or the manufacturer
   c. Report the data regarding who is detecting ADEs and who reports, documents, and manages the ADEs
   d. Provide trending data on the basis of either drug or drug class and by specialty units
   e. Benchmark the hospital's ADEs against itself in previous years and compare them with the data from other hospitals published in the biomedical literature. Total ADE data can be reported according to the following:
      i. Total number of ADEs
      ii. ADEs per admission
      iii. ADEs per patient
      iv. ADEs per patient-days
      v. ADEs per doses dispensed
      vi. ADEs per doses administered

10. A popular method of reporting ADEs is by the total number of admissions, with an acceptable benchmark of 2.5%–10% (e.g., a hospital with 10,000 admissions reporting 1000 ADEs would have a 10% ADE reporting rate). ADE benchmarks are difficult to determine because of the many variables that affect the reporting methods, such as the ADE definition used by the facility or the definition used by the reporter, the number of clinical pharmacists available to report, the vigilance and emphasis of the reporting systems, and the use of technology or reports to increase reporting.

E. Documenting ADRs and ADEs in the Patient's Medical Record
  1. Allergy data are always documented in the patient's medical record and are required in the patient profile. Preferably, the specific medication that caused the allergy, the type of reaction, and when the allergy occurred should be documented.
  2. The EHRs where these data are often found were incentivized by "meaningful use." The Centers for Medicare & Medicaid Services program is meant to assist in adopting EHR technology, including advanced data sharing and a focus on quality of care. In 2018, the term *meaningful* use was changed to *promoting interoperability*.
  3. A drug-induced allergy can be an ADR or an ADE, depending on severity.
     a. It is paramount to report and document ADE data in the patient's medical record for the same reason as documenting allergy data to prevent recurrence with the same drug or a drug from the same or similar drug class, and to mitigate risk when the same drug may need to be used again or to mitigate risk when other medications that can cause the same adverse event are used.
     b. If possible, a true allergy and an ADE/ADR should be differentiated between within the EHR.
  4. ADR and ADE data should be recorded in the electronic medical record and maintained in the record indefinitely.
     a. For mild ADRs: When the same medication is prescribed, the CDS system can be set to alert the prescriber, or the data can be retrievable for review but without prompting the clinician (e.g., lisinopril-induced hypotension).
     b. For moderate ADRs: When the same drug is prescribed, the EHR, including the CDS system, can be programmed to highlight or warn the prescriber or require a text response with an explanation for its continued use.
     c. For severe ADRs and ADEs: When the same drug is prescribed, the EHR, including the CDS system, can be programmed to cause a hard stop and prevent the drug from being prescribed or a hard stop requiring a prompt with an explanation for use (e.g., isoniazid-induced hepatotoxicity).

F. Methods of Medication Error and ADR or ADE Surveillance
  1. ADEs can be detected prospectively and retrospectively.
     a. Pharmacists may detect ADEs prospectively while on patient care daily rounds, or from communication with patients while administering medication histories or transitions of care (e.g., ICU to step-down) or during discharge counseling.
     b. An example of CDS is automated triggers used for prospective surveillance of events (i.e., before an event has occurred). Pharmacists may also detect ADEs retrospectively through medical record reviews or during medication histories or chart reviews (i.e., after an event has occurred, so limited opportunity for intervention).
  2. Although CDS is reinforced by the literature on reducing medication errors, it must be weighed against the potential for alert-driven interventions to cause "alert fatigue."
     a. No consensus definition exists for alert fatigue; however, it can be conceptualized as how increasing the number of alerts may result in decreased attention to interacting with the alerts.
     b. Given the lack of definition, it is difficult to measure alert fatigue. Potential metrics may include the following:
        i. Sensitivity, specificity, positive predictive value, and negative predictive value of alerts
        ii. Number of alerts overridden

        iii. Number of alerts inappropriately overridden
        iv. Patient harm associated with inappropriately overridden alerts
    c. This fatigue is associated with an increased risk of preventable ADEs in a critically ill population.
    d. Further research is needed on how to use alerts and other types of CDS more effectively, specifically in the ICU.

3. Retrospective incident voluntary reporting is an ethical obligation of all health care professionals.
    a. Voluntary reporting is the primary source of event identification for most institutions; however, events are grossly underreported.
    b. Typically, safety pharmacists are responsible for aggregating these data. These aggregate reports are reviewed by the ADE committee for the institution. Possible prevention methods are determined by the committee. This is a retrospective evaluation because events are typically evaluated when there is allotted time, which is often when the patient is discharged from the hospital. This can be a prospective method if real-time evaluation is an option.
    c. Trigger/tracer drugs
        i. ADEs can be detected using a CDS system within an EHR for *trigger* or *tracer drugs* – these terms are used synonymously. Trigger or tracer drugs are drugs that are routinely prescribed to treat ADEs, such as antidotes, or physiologic antagonists or agents for gastric decontamination. These triggers prompt a targeted medical record review. Box 2 provides examples.
        ii. The CDS system can be programmed with a list of tracer drugs so that when prescribers order a tracer drug, they are asked whether the order is for an ADE and, if so, what type of ADE occurred. The potential ADE can then be reported and managed by the clinical pharmacist.
        iii. One of the benefits of this system is that it captures ADEs that might not have been reported, especially when a clinical pharmacist may not be present on the unit or on daily patient care rounds, and it allows for more physician-reported ADEs.

Box 2. Examples of Medications Used as Triggers or Tracers to Aid in Reporting Adverse Drug Events

1. Acetylcysteine (enteral, injection)
2. Activated charcoal suspension
3. Atropine (injection)
4. Benztropine
5. Dantrolene
6. Diphenhydramine
7. Diphenoxylate/atropine
8. D50W
9. Digoxin immune FAB
10. Epinephrine 0.15/0.3 mg autoinjector
11. Fidaxomicin
12. Flumazenil
13. Glucagon
14. Hydrocortisone (injection, topical)
15. Loperamide
16. Naloxone
17. Phytonadione
18. Prednisone
19. Protamine
20. Prothrombin complex concentrate
21. Sodium zirconium cyclosilicate
22. Vancomycin (enteral, rectal)

$D_{50}W$ = dextrose 50% in water.

  d. Therapeutic drug concentration and abnormal laboratory value monitoring can be another source for ADE detection. The pharmacy may design daily reports that contain all the abnormal drug serum concentrations such as the phenytoin, digoxin, lithium, vancomycin, and aminoglycoside concentrations, or other laboratory monitoring values (e.g., lisinopril and potassium). The clinical pharmacist can then review all cases of supratherapeutic concentrations and laboratory abnormalities by performing a targeted medical record review for ADEs. Although these are basic CDS functions that include medications and laboratory values as the knowledge for the alert, more advanced, "smarter" alerts are being used that include risk scoring–based approaches that help prioritize the pharmacist's reviews.
  e. Identified events must be confirmed for causality. Many instruments can help link the drug with the event. Structured instruments create a more reliable and valid assessment. A sample ADE form with the Naranjo criteria for causality determination is provided in Appendix 1. This is the most commonly used ADR causality instrument, though its reliability and validity in the critically ill population need improvement. Another instrument specific for drug-induced liver injury is the RUCAM. Causality assessment includes temporal sequence, dechallenge (removal of the suspect drug), rechallenge (reintroduction of the suspect drug), evaluation of other causes, objective evidence that is available or obtained, and history of a reaction to a similar drug.
4. Prospective
  a. Direct observation
    i. One method of medication error detection is through direct observation; this can be accomplished using the medication pass method, in which the pharmacist observes nurses in the medication administration process and notes any errors that occur.
    ii. Direct observation provides the unique advantage of capturing medication administration errors that are not typically identified with other detection methods. Other examples of direct observation include nurses observing nurses or physicians observing physicians during medication administration. This is considered prospective because observation occurs in real time but errors are evaluated later.
    iii. A potential limitation of direct observation is that if an individual is aware of being observed, the individual may change behavior to be "optimal" (i.e., the "Hawthorne effect").
  b. CDS with alert generation can be used for prospective or real-time surveillance.
    i. Prescribing – Providers can be notified of high-risk scenarios during the ordering process in order to prevent medication errors, such as prescribing enoxaparin for a patient with a CrCl less than 30 mL/minute. Alerts during medication ordering should be used judiciously and created with greater precision to avoid alert fatigue
    ii. Administering—Dosing calculators integrated into the EHR for nursing-driven protocols (eg, insulin infusions or sliding scales, anticoagulant infusions).
    iii. Order verification – Pharmacists receive preventive alerts during order verification to avoid medication errors and the potential for ADEs (e.g., drug-drug interactions, duplicate therapy).
    iv. High-risk scenarios in real time – Pharmacists may receive advanced alerts outside order verification, indicating when a patient is initiated on a drug, but the patient's clinical scenario presents a risk (e.g., patient receiving an epidural and initiated on a systemic anticoagulant).

G. Role of Technology in Mitigating ADEs and ADRs
1. Role of artificial intelligence in medication use process (J Am Coll Clin Pharm. 2025;8(4):302-310)
  a. Prescribing
    i. Incorporation of patient-specific clinical data to develop personalized treatment plans, including pharmacogenomics, to reduce alert fatigue
    ii. Integration of diagnostics and patient data to reduce time to diagnosis

b. Dispensing
    i. Identification of “problem orders” before pharmacist review
    ii. Prediction of drug shortages and development of mitigation strategies
c. Administration
    i. Incorporation of technology (eg, continuous glucose monitor, smart pump)
d. Monitoring
    i. Identifying clinically relevant drug-drug interactions in the ICU setting
    ii. Identifying the rate of ADEs and ADRs specific to the ICU setting

Patient Cases

2. Which best classifies the degree of severity of an ADE in a patient who develops enalapril-induced asymptomatic hyperkalemia with no noted ECG changes (K 5.7 mEq/L) managed with one dose of sodium zirconium cyclosilicate?

    A. Mild.
    B. Moderate.
    C. Severe.
    D. Life threatening.

3. Which best classifies the degree of severity of an ADE in a patient who is in the geriatric psychiatry unit and develops intravenous haloperidol-induced torsades de pointes that is successfully treated with intravenous magnesium and managed with additional monitoring in the cardiac care unit and telemetry?

    A. Mild.
    B. Moderate.
    C. Severe.
    D. No classification.

Questions 4 and 5 pertain to the following case.
M.S., a 77-year-old patient residing in a nursing home, has taken lisinopril 10 mg daily for the past 3 months. They are admitted to the ICU with lisinopril-induced angioedema and present with severe tongue swelling, stridor, and shortness of breath that necessitated a tracheotomy. They had no history of allergies and did not miss any doses of lisinopril.

4. Which best describes this patient’s reaction to lisinopril?

    A. ADE.
    B. Preventable ADE.
    C. Medication error.
    D. Preventable ADR.

5. Which best classifies the degree of severity of this patient’s ADE to lisinopril?

    A. Mild.
    B. Moderate.
    C. Severe.
    D. No classification.

III. 2017 SCCM CLINICAL PRACTICE GUIDELINE: SAFE MEDICATION USE IN THE ICU

A. Structure of Guideline
   1. Developed in 2017 with literature searches up to the end of 2015, focused on 34 PICO (population/problem/patient, intervention/indicator, control/comparator/comparison, and outcomes) questions, including data on adult and pediatric ICU patients
   2. First clinical guideline to address safe medication use in the ICU. Identified that rigorous research to guide practice is still needed in many areas
   3. Three key components: environment and patient, medication use process, and patient safety surveillance systems
   4. Recommendations based on GRADE system (quality of evidence: A = high to D = very low; strength of recommendation: 0 = no recommendation, 1 = strong, 2 = weak)

B. Highlights of Environment and Patient
   1. ICU patients have different risk factors for ADEs, and the severity of medication errors is higher than with general care (non-ICU) patients (both grade C).
   2. Guidelines suggest that educational efforts should be used to reduce medication errors in the ICU (2C).
   3. No recommendation was provided regarding disclosure of medication errors/ADEs to patients and/or family members, because of lack of data, but this is recommended by the National Quality Forum.

C. Highlights of Medication Use Process
   1. Four stages of process (prescribing, dispensing, administration, monitoring)
   2. Prescribing
      a. Guidelines suggest implementing computerized provider order entry to decrease medication errors and preventable ADEs (2B). Some data support medication error reduction, but evidence is conflicting, with a decrease in omission errors but an increase in duplicate order errors.
      b. Guidelines suggest using CDS systems to decrease the number of medication errors and ADEs (2C).
         i. CDS systems are tools designed to enhance clinician decision-making (e.g., allergy, drug-drug interaction, dosing recommendations).
         ii. Trigger-initiated CDS alerts cause a concern for alert fatigue that requires a balance between sensitivity and specificity because of lack of patient-specific considerations (e.g., ICU level of care).
      c. Guidelines suggest using protocols/bundles to reduce medication errors/ADEs (2B).
      d. No recommendation is provided regarding the use of medication reconciliation to decrease medication errors and ADEs in ICU patients or for transitions of care.
   3. Dispensing
      a. Guidelines recommend compliance with safe medication concentration practices (e.g., premade mixes, standardized medication concentrations within institution) to reduce the number of medication errors and potential ADEs (1B).
      b. Guidelines suggest use of automated packaging and dispensing of medications to reduce medication errors/ADEs versus non-automated methods (both 2C).
      c. Guidelines suggest use of medication labeling practices (e.g., tall man lettering) for sound-alike look-alike drugs to reduce medication errors (2B).

4. Administration
    a. Guidelines suggest use of bar code medication administration (BCMA) to reduce medication errors and/or ADEs in the ICU (2C).
        i. Conflicting evidence on benefit, though data largely suggest reduction in medication errors and potential ADEs
        ii. One limitation of BCMA is that workarounds will reduce effectiveness.
    b. Guidelines suggest smart intravenous infusion pumps be used to reduce the rate of medication errors and ADEs (2C).
        i. Evidence is conflicting on the use of the guardrails and the types of errors evaluated.
        ii. Concern for auditory alarm fatigue exists with smart pumps, especially in the context of other auditory alarms in the ICU.

D. Highlights of Patient Safety Surveillance Systems
1. Guidelines recommend use of direct observation as an active medication surveillance system to identify the medication errors (1A).
2. Guidelines suggest nontargeted chart review to detect ADEs, versus voluntary reporting, to increase the number of ADEs identified, though this is a resource-intensive process (2C).
3. Guidelines suggest targeted chart review to increase ability to detect ADEs compared with voluntary reporting (2B). Strategies include evaluation of only a specific section of the patient's medical record (e.g., ICU discharge note, laboratory abnormalities in the setting of certain drugs) or trigger medications.
4. Guidelines suggest patient and family reporting at or after ICU discharge to improve medication error and ADE detection (2C). This includes formalization of a process for interviewing patients or family members about possible medication errors or ADEs that occurred while the patient was in the ICU.

IV. DRUG INTERACTION SURVEILLANCE AND PREVENTION

A. Definition
1. When the effects of one drug can be changed by the presence of another substance (e.g., medication, dietary), which may be intentional, clinically insignificant, or harmful and potentially life threatening
2. Drug-related toxicity may be preventable and may require therapeutic intervention (e.g., monitoring, discontinuation of medication).

B. A documented drug interaction with known outcomes can be considered a medication error, a preventable ADE, or an ADR, depending on clinical context.

C. Drug infusion compatibility interactions (e.g., Y-site) are more common in the ICU because of increased likelihood of prolonged infusions.

D. Drug interaction databases include Lexicomp, IBM Micromedex, Epocrates, Clinical Pharmacology, Hansten and Horn's *Drug Interaction Analysis and Management,* Stockley's *Drug Interactions,* and *PDR Drug Interactions*. Many EHRs include Medi-Span and First Databank.
1. Most compilation databases have drug interaction software in which the pharmacist can provide a list of drugs and the database will provide the type of interaction and severity. Of note, agreement between databases for severity of interactions is estimated to be less than 50%.
2. Databases use different methods to assess severity of drug interactions.
3. Clinical judgment should always be applied when assessing drug interactions.

E. Safety Measures to Avoid/Manage Drug Interactions
    1. Pharmacist review and validation
        a. Pharmacists are highly trained in pharmacology and drug interactions and are expected to apply advanced analysis and clinical qualification/management of drug interactions.
        b. Limitations include that not all medications a patient uses are filled by one pharmacy as well as the lack of potential data that can be pulled from a patient's EHR that can inform the existence and clinical relevance of drug-drug interactions.
    2. Using EHRs with CDS alerts that detect drug interactions
        a. Examples include passive pop-up warnings (e.g., alerts), active alerts with soft stops (e.g., documented allergy of nausea), and active alerts with hard stops (e.g., documented allergy of anaphylaxis).
        b. May prompt prescriber or pharmacist during order verification with a high frequency of alerts, leading to desensitization (i.e., alert fatigue)
        c. Despite the potential benefits of CDS, within the ICU patient population overrides are common, with a rate of around 80%, depending on the alert type. Inappropriate overrides of CDS alerts within the ICU are associated with an increased risk of patient harm.
        d. Drug-drug interaction alert fatigue can be managed by reducing the alert number, using severity or tiering of the interaction as a criterion for alert selection.
    3. Education as a method to prevent drug interactions (e.g., lectures, patient care rounds)

F. How to Evaluate Drug Interaction Cases
    1. Assessing causation of a drug interaction includes a temporal relationship, consideration of the pharmacologic properties of the object and precipitant drug, patient factors and disease states, the possible contribution of other drugs, and, when possible, a positive dechallenge. The temporal sequence is the key element in these considerations to help determine the cause.
    2. ADE nomograms such as the Naranjo nomogram are designed to evaluate ADEs, not drug-drug interactions; therefore, they should not be used to evaluate drug-drug interaction cases.
    3. The drug interaction probability scale may be used to determine drug-drug interaction causation, including the adverse outcomes in a specific patient (Appendix 2).
        a. The drug interaction probability scale is patterned after the Naranjo ADR probability scale. A series of 10 questions related to the drug interaction are assessed with "yes," "no," "unknown," or "not available" answers and then scored and tabulated. The total score determines the probability of the drug-drug interaction occurring in the patient as follows:
            i. Highly probable: More than 8
            ii. Probable: 5–8
            iii. Possible: 2–4
            iv. Doubtful: 2 or less
        b. When using the drug interaction probability scale, the evaluator must have comprehensive knowledge of the pharmacologic properties of both the object and the precipitator drug, especially their pharmacokinetic and pharmacodynamic properties and their mechanisms of drug action and mechanisms of drug interactions, which can be a limitation to its use.

V. FORMULARY PROCESS

A. The drug formulary should be comprehensive and include all the medications needed for patient care.

B. The Joint Commission medication management standard requires hospitals to develop and approve the criteria for selecting medications into the drug formulary.

C. At a minimum, the drug selection criteria should include the following:
   1. Indications for use (FDA label approved and off-label)
   2. Efficacy and effectiveness
   3. Drug interactions
   4. Adverse effects
   5. Sentinel event advisories
      a. May include REMS (Risk Evaluation and Mitigation Strategies) for certain medications (if one exists)
      b. This FDA medication safety program is for medications with known significant safety concerns (e.g., birth defects, hepatotoxicity) that require an understanding of its risks and necessary interventions that are preventive to safely use the medication.
   6. Cost acquisition and total cost of care: This is a good application of the budget impact analysis. Ideally, if cost-effectiveness and cost-utility analyses are also available, they should be considered; however, they are typically not available this early in the drug approval process.

D. The P&T committee is responsible for maintaining the drug formulary and ensuring that new medications that can improve patient care are reviewed for formulary inclusion.

E. Critical care pharmacists should be cognizant of new medications and new medication dosage forms that may be used to improve the treatment of critically ill patients. Critical care pharmacists should collaborate with intensivists and other experts to request the addition or deletion of a drug from the formulary.

F. Box 3 lists the elements of a drug evaluation monograph that should be reviewed before a drug is approved to the hospital formulary.

Box 3. Elements of a Drug Evaluation Monograph

Brand name
Generic name
Manufacturer
Therapeutic classification
FDA status: Prescription, nonprescription, or controlled substance
Look-alike sound-alike names with any other FDA label-approved medications
Look-alike sound-alike names with any other FDA label-approved medications on the formulary
Date of FDA label approval
FDA rank (priority or standard)
FDA label-approved indication
Unlabeled indications
Potential unlabeled uses
Similar agents not on the formulary
Similar agents on the formulary
How the drug can be used when applied to available national guidelines
How the drug can be used when applied to hospital guidelines, protocols, or pathways
Dosage form
Dosage strength
Mechanism of action
Absorption
Distribution
Metabolism
Excretion
Common ADRs or ADEs
Significant or life-threatening ADRs or ADEs
Boxed warnings, including Risk Evaluation and Mitigation Strategies
Precautions
Contraindications
Drug-drug interactions
Drug-food interactions
Drug-laboratory test interactions
IV incompatibilities
IV compatibilities
Pregnancy category
Use during breastfeeding
Dosage regimen recommendations
Dosage regimen recommendations for special populations such as children, older adults, persons with renal and hepatic impairment, and persons undergoing dialysis
Routes of administration and/or limitations
Any special administration techniques (prescriber certification, smart pump limitations)
Preparations available
Storage and stability considerations
Any availability concerns (specialty pharmacy restrictions)
Critical review of pertinent clinical trials with salient critique and conclusions
Critical review of comparison trials with similar or alternative agents
Cost analysis including annual projected costs and reimbursement
Economic evaluations
Pharmacoeconomic analyses available
Budget impact analysis specific to the institution
Reimbursement from third-party payers
Are there any severe medication errors or sentinel events with this agent?
Does this medication need to be stored under specific circumstances to avoid medication errors or mix-ups?
Does this medication require tall man lettering labeling or precautionary or high-risk labeling to avoid potential medication errors or mix-ups?
Is the manufacturer-provided labeling considered clear and safe for dispensing?
Is an abuse potential associated with the use of this medication?
Patient education requirements
Will this agent replace an existing agent, and should a formulary deletion take place?
Reason why or why not this medication should be included in the formulary Recommendation for addition to the formulary
References

ADE = adverse drug event; ADR = adverse drug reaction; IV = intravenous(ly).

G. A comprehensive literature review should be used to determine a drug's efficacy and toxicity profile, with stronger levels of evidence guiding decisions regarding whether to add to the formulary.
   1. Prospective double-blind randomized controlled trials should have greater weight than retrospective cohort and case-control studies, though it is important to critique all types of studies regarding limitations to understand the strength of a study.
   2. Meta-analyses may also be considered, depending on the number and criteria for included studies.
   3. Case reports should be used only when no other evidence is available.

H. Pharmacists developing the drug evaluation monograph must be adept in drug literature evaluation and pharmacoeconomics.

I. Drug evaluations should contain references to evidence, and opinion statements should be clearly noted.

J. Internal prescribing data may also be used in formulary decisions, such as
   1. Quantity of drug used over a specified time
   2. Medication use evaluation data
   3. ADR data
   4. Medication error data

K. Because trials leading to the approval of new drugs are often limited in their sample size and ability to detect ADEs (especially more long-term effects), it is prudent to observe safety profiles of new drugs before considering addition to the formulary, if possible. For example, some drugs may cause life-threatening toxicity such as hepatic failure at a rate of 1:20,000 patients, thus requiring more than 100,000 postmarketing patient exposures before generating a signal of toxicity.

L. Drugs may be added to the formulary without any use restrictions, or they may be added with restrictions, such as the following:
   1. Restriction to specific patient population meeting use criteria (e.g., level of monitoring, other therapies tried)
   2. Restriction to specific patient population at low risk of an ADE (e.g., hepatotoxicity)
   3. Restriction to specific providers

M. Modifications to the EHR should be implemented on the basis of formulary additions, which include appropriate CDS such as dosing and recommended monitoring, as well as information on formulary restrictions.
   1. Education of formulary additions is critical for appropriate use, including appropriate indications and monitoring.
   2. In the event of a drug shortage for the formulary addition, the P&T committee should provide prompt recommendations to manage limited supply.

N. Once a drug is admitted for formulary approval, periodic assessments in the form of a medication use evaluation or reviews of use (including compliance with institutional guidelines), cost, safety, and efficacy should be made, preferably within 3–6 months and again in 1 year. The goal is to determine the effectiveness of the drug. Effectiveness is the use of a drug in the real-world setting outside a randomized controlled trial and differs from the efficacy reviewed before adding the drug to the formulary. Examples of approvals that may require quicker reevaluation (e.g., 3 months) are those with very limited efficacy data, concern for lack of compliance with formulary restrictions, high risk of safety events, or medications with a very high cost.

O. All drugs on the formulary within a class should be assessed annually or more often when there is an important change in prescribing information, when a landmark trial or publication affects the drug's use, or when new FDA label-approved agents are available within the drug class. Medication assessments typically prompt updates and modifications to the drug's current use.

Patient Case

Questions 6–8 pertain to the following case.

Your institution is considering adding angiotensin II (ATII) to the hospital formulary. Angiotensin II is a non-catecholamine vasopressor that is FDA approved for increasing blood pressure in distributive shock after publication of the ATHOS-3 trial. The trial, which compared intravenous ATII with placebo once patients received a certain dose of vasopressors, showed that patients who received ATII reached a hemodynamic goal more often than placebo, with no differences in mortality or safety outcomes. Your hospital formulary currently includes the catecholamine vasopressors and vasopressin. A particular concern of your institution is the cost of ATII therapy and adherence to formulary restrictions.

6. When creating the drug evaluation monograph for adding ATII, which recommendation would be most appropriate to include?
   A. Remove vasopressin from the hospital formulary to make room for ATII.
   B. Addition of statement that ATII decreases mortality in patients with distributive shock.
   C. Addition of both the intravenous and oral formulations of ATII to the formulary.
   D. Restrict use to patients who received the same dose of vasopressors as those included in the ATHOS-3 trial.

7. In considering adding ATII to the formulary, which characteristic of your institution would be most important to consider?
   A. Data from ATHOS-3 suggesting its clinical superiority to other FDA-approved medications.
   B. How often you encounter patients who require several vasopressors for management of distributive shock.
   C. The increased risk of ADEs associated with the use of ATII.
   D. Data analyses suggesting the cost-saving benefits of ATII compared with other FDA-approved medications.

8. Angiotensin II was approved by your institution last December, after presentation to the P&T committee. Which best depicts the month in which the first medication use evaluation should be completed?
   A. March of this year.
   B. June of this year.
   C. October of this year.
   D. December of this year.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: A**

Indirect costs occur from loss of employment or productivity as the result of illness (Answer A is correct). Effects from stress would be considered an intangible cost (Answer B is incorrect). Costs from fentanyl and transportation would be considered direct costs (Answers C and D are incorrect).

2. **Answer: A**

A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring. Enalapril-induced hyperkalemia managed by one dose of sodium zirconium cyclosilicate did not require aggressive interventions, nor did it lead to any patient harm; however, it did require increased laboratory monitoring, making Answer A correct and Answers B, C, and D incorrect.

3. **Answer: C**

A severe ADE results in patient harm, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, which did occur in this case (Answer D is incorrect). Haloperidol-induced torsades de pointes is a life-threatening dysrhythmia (end-organ damage) that required aggressive and successful management with intravenous magnesium and patient transfer to a higher level of care (Answer C is correct). A moderate ADE is defined as an ADE that resulted in the need for aggressive intervention with antidotes or an increased length of hospital stay (Answer B is incorrect). A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring, which did not occur in this case, making Answer A incorrect.

4. **Answer: A**

Because this patient developed lisinopril-induced angioedema, had no history of allergy to angiotensin-converting enzyme inhibitors, and missed no lisinopril doses, his ADE was not a preventable error (Answer B is incorrect). This was also not a medication error, given the information provided (Answer C is incorrect). There is no such thing as a preventable ADR because an ADR occurs from normal use of a medication and is therefore by definition nonpreventable (Answer D is incorrect). Therefore, this would be considered an ADE (Answer A is correct).

5. **Answer: C**

A severe ADE is defined as an ADE that results in patient harm, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, with the probable ADE causality nomogram score. Because this patient developed life-threatening lisinopril-induced angioedema and needed a tracheotomy, resulting in patient harm, hospitalization, and transfer to a higher level of care, this case meets the criteria for a "severe" ADE, making Answer C correct and Answers A, B, and D incorrect.

6. **Answer: D**

When considering what to include in a drug evaluation monograph for formulary addition, it is important to consider the data analyses available supporting its use. According to what was provided in the case, ATII was only compared with placebo (Answer A is incorrect), did not show any significant differences in mortality (Answer B is incorrect), and was studied in an intravenous formulation (Answer C is incorrect). Answer D is correct because considering the inclusion criteria for the study would be helpful for formulary restriction, especially given the institutional concern of cost.

7. **Answer: B**

Considerations for formulary addition are important before P&T committee proposals. According to the ATHOS-3 trial, ATII was not compared with other currently available medications (Answer A is incorrect), there were no significant differences in ADEs (Answer C is incorrect), and no data analyses are available suggesting that ATII is cost-saving (Answer D is incorrect). Considering how often you might require the use of ATII would be an important initial consideration (Answer B is correct).

8. **Answer: A**

The first medication use evaluation is recommended to occur within 3–6 months of formulary addition. Therefore, March would be the most appropriate month (Answer A is correct). Although June would fall in the

3- to 6-month range, given the novelty of this agent and its cost, it would be important to conduct a medication use evaluation as soon as possible (Answer B is incorrect). October and December would be too long to wait for an evaluation to be performed (Answers C and D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: B**

The cost of a medication would be considered a variable medical cost (Answer B is correct). The cost of the lights in the clean room would be considered a fixed medical cost (Answer A is incorrect). The time resulting in loss of work for a patient requiring this medication would be considered an indirect cost (Answer C is incorrect). Additional use of blood products after administration of this medication would be considered an incremental cost (Answer D is incorrect).

2. **Answer: B**

Given the need to consider efficacy and cost, a cost-effectiveness analysis would be the best type of analysis (Answer B is correct). A cost-benefit analysis would be used if your institution were purely interested in a monetary outcome (Answer A is incorrect). A cost-minimization analysis would only evaluate the difference in costs between these medications (Answer C is incorrect). A cost-utility analysis includes the patient perspective, which was not a focus of this evaluation (Answer D is incorrect).

3. **Answer: D**

A preventable ADE, by definition, is a medication error that occurs and reaches the patient to cause harm because of a breach of standard professional behavior or practice. The patient had a documented history of cefuroxime allergy with shortness of breath but still received ceftriaxone and developed another life-threatening anaphylactic reaction; this is a medication error, and the anaphylactic reaction is the harm. Allergy cross-reactivity between cefuroxime and ceftriaxone is well documented for patients with a history of shortness of breath because of similarity in side chains; therefore, this is a preventable ADE (Answer D is correct). Although this case of ceftriaxone-induced life-threatening anaphylaxis is an ADE, a preventable ADE best describes this case (Answer C is incorrect). In general, *ADRs* and *side effects* are synonymous terms, and a ceftriaxone-induced allergy is an ADR; however, a preventable ADE best describes this case (Answers A and B are incorrect).

4. **Answer: D**

Prothrombin complex concentrate would be the best tracer for an ADE associated with apixaban (Answer D is correct). Coagulation factor VIIa would not be effective for this indication (Answer A is incorrect). Phytonadione would be an appropriate tracer for a warfarin-induced bleeding event (Answer B is incorrect). Protamine would be an appropriate tracer for a heparin- or enoxaparin-induced bleeding event (Answer C is incorrect).

5. **Answer: C**

The guidelines provide several recommendations, with only one having a strong recommendation, which is based on the dispensing of medications and streamlining them as only being from the pharmacy (Answer C is correct). The other potential answers are potential opportunities to improve medication safety but are based on weak recommendations (Answers A, B, and D are incorrect).

6. **Answer: B**

The guidelines suggest (not recommend) that patient/caregiver-reported outcomes be integrated into routine patient care (Answer A is incorrect). Data analyses on the benefit of these interactions are limited to non-ICU environments, though the theoretical benefits listed in Answers C and D may be true (Answers C and D are incorrect; Answer B is correct).

7. **Answer: B**

To determine the probability of a drug interaction between meropenem and valproic acid, the drug interaction probability scale should be used (Answer B is correct). A drug interaction database would provide general information and is not a patient-specific evaluation (Answer A is incorrect). The Naranjo nomogram investigates the likelihood of an ADE but is not specific to a drug interaction (Answer C is incorrect). The RUCAM evaluates the likelihood of drug-induced liver injury (Answer D is incorrect).

8. **Answer: C**

Broad-spectrum antimicrobials should be restricted to the appropriate clinicians with expertise in this area (Answer C is correct). Restricting use to intensivists would not be appropriate because non-ICU patients may require this agent (Answer A is incorrect). Although FDA approved only for complicated UTIs, restriction to pneumonia would not be appropriate (Answer B is incorrect). Cardiac monitoring is not required for this medication (Answer D is incorrect).

Appendix 1. Adverse Drug Event Reporting Form

ADE#:

ADVERSE EVENT INFORMATION

1. NAME	2. PATIENT ID #	3. LOCATION	4. AGE	5. SEX	6. REACTION ONSET DATE
					7. DATE OF REPORT

8. DESCRIBE REACTION AND ITS MANAGEMENT. (Continue on the back if necessary. Use Arial Narrow Font Size 10)

9. Check all appropriate

	Patient died
	Reaction treated with drug
	Resulted in or prolonged inpatient hospitalization
	None of the above

10. Did event abate after discontinuing the drug?

	YES
	NO
	MAYBE

11. Was patient's electronic allergy/ADE profile updated?

	YES
	NO

(If no, please explain on second page)

12. RELEVANT TESTS/LABORATORY DATA

SUSPECTED DRUG(S) INFORMATION

13. SUSPECTED DRUG(S) Give manufacturer & lot number for vaccine/ biologics/ biotechnological		17. DATES OF ADMINISTRATION
14. DOSE AND FREQUENCY	15. ROUTE OF ADMINISTRATION	18. DURATION OF ADMINISTRATION

16. INDICATION(S) FOR USE

CONCOMITANT DRUG HISTORY

19. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat the reaction)

20. OTHER RELEVANT HISTORY (e.g., diagnoses, medical history, allergies, pregnancy)

INITIAL REPORTER (In confidence)

JCAHO Standard PI. 2.20 states that all serious adverse drug reactions are intensely analyzed. Standard MM. 6.20 maintains that the responsible individual complies with internal and external reporting requirements for adverse drug reactions. (2006 Comprehensive Accreditation Manual for Hospitals)

Please take the time to complete this form for each suspected adverse drug reaction, and forward it to the Department of Pharmacy for reporting at the next Adverse Drug Reaction Subcommittee meeting.

Date	Time	MD Notified about Possible ADR	Pharmacist's Signature

Submission of a report does not necessarily constitute an admission that the drug caused the reaction

NAME AND ADDRESS OF REPORTER (Including zip code)

TELEPHONE NO. (Include area code)

HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?

	YES
	NO

Appendix 1. Adverse Drug Event Reporting Form *(continued)*

KJMC ADVERSE DRUG EVENT REPORTING FORM
Modified Naranjo Criteria for Causality (also called ADR Probability Scale)

ASSESSMENT	YES	NO	DON'T KNOW (not conducted, not reported)	SCORING SYSTEM
1. Are there previous reports (in the literature) of this reaction? (If no, please provide documentation of search strategy)	+1	0	0	Based on the total score, circle the term that best defines this ADR: ≥ 9 Definite 5–8 Probable 1–4 Possible ≤ 0 Doubtful
2. Did the ADR appear after the suspected drug was administered, confirming a temporal relationship? (If no, please explain)	+2	-1	0	
3. Did the ADR improve when the drug was discontinued or a specific antagonist was administered? (If no, please explain)	+1	0	0	
4. Did the ADR reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could have caused the ADR? (If yes, please explain)	-1	+2	0	
6. Did the ADR reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood or other fluids in toxic concentrations?	+1	0	0	
8. Evaluate the dose-response relationship; was the ADR more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patients have a similar reaction to the same or similar drugs (i.e., same drug class) in a previous exposure?	+1	0	0	
10. Consider signs, symptoms, and laboratory values other than drug concentrations. Was the ADR confirmed by objective evidence?	+1	0	0	
TOTAL SCORE				

Source: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

Appendix 2. Drug Interaction Probability Scale

The drug interaction probability scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event. It is patterned after the Naranjo ADR probability scale (Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45).

Directions

- Circle the appropriate answer for each question and add up the total score.
- Object drug = Drug affected by the interaction.
- Precipitant drug = Drug that causes the interaction.
- Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (e.g., no dechallenge; dose not changed).

Questions	**Yes**	**No**	**NA/Unk**
1. Are there previous credible reports of this interaction in humans reported in the literature?	+1	–1	0
2. Is the observed interaction consistent with the known interactive properties of the precipitant drug?	+1	–1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	–1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset or offset)?	+1	–1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip question 6)	+1	–2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	–1	0
7. Are there reasonable alternative causes for the event?[a]	–1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	–1	0

---

[a] Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (e.g., age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score _____ Highly Probable: > 8
Probable: 5–8
Possible: 2–4
Doubtful: < 2

INFECTIOUS DISEASES I

JACOB SCHWARZ, PHARM.D., MBA, FAZPA, BCIDP, BCCCP, BCPS

MAYO CLINIC
PHOENIX, AZ

INFECTIOUS DISEASES I

JACOB SCHWARZ, PHARM.D., MBA, FAZPA, BCIDP, BCCCP, BCPS

MAYO CLINIC
PHOENIX, AZ

Learning Objectives

1. Develop risk factor–based empiric antibiotic regimens for patients with suspected ventilator-associated pneumonia.
2. Develop empiric and definitive antimicrobial therapy plans for patients with central line-associated bloodstream infections and catheter-related urinary tract infections.
3. Differentiate between location of intra-abdominal infections and respective empiric antimicrobial therapy, including the role of antibiotics in patients with acute pancreatitis.
4. Develop a definitive management strategy for critically ill patients with severe *Clostridioides difficile* infection.
5. Describe the role of pharmacotherapy and recommend appropriate therapy for patients with severe postoperative wound infection or severe cutaneous infections.
6. Identify a disease-specific and supportive care management plan for critically ill patients with severe influenza and novel severe acute respiratory syndrome coronavirus 2.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
CAUTI	Catheter-associated urinary tract infection
CDI	*Clostridioides difficile* infection
CLABSI	Central line–associated bloodstream infection
COVID-19	Coronavirus disease 2019
CVC	Central venous catheter
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IVIG	Intravenous immunoglobulin
MDRO	Multidrug-resistant organism
MICU	Medical intensive care unit
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MV	Mechanical ventilation
NHSN	National Healthcare Safety Network
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Reverse transcription polymerase chain reaction
SICU	Surgical intensive care unit
SIRS	Systemic inflammatory response syndrome
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.
K.P., a 38-year-old otherwise healthy woman, was involved in a motor vehicle collision, sustaining a traumatic brain injury and severe chest injuries requiring endotracheal intubation and mechanical ventilation (MV). After being in the trauma intensive care unit (ICU) for 96 hours, a new infiltrate is noted on her chest radiograph, as well as a temperature of 101.9°F (38.8°C), a white blood cell count (WBC) of 15 x 10^3 cells/mm^3, and macroscopically purulent sputum. K.P. is hemodynamically stable. Accordingly, your team decides to obtain a bronchoscopic bronchoalveolar lavage (BAL) of the affected lung field to assess for ventilator-associated pneumonia (VAP), where your local ICU MRSA prevalence is less than 10%.

1. Which is the most likely causative pathogen of K.P.'s suspected VAP?
   A. *Acinetobacter* spp.
   B. Methicillin-resistant *Staphylococcus aureus* (MRSA)
   C. Multidrug-resistant *Pseudomonas aeruginosa*
   D. *Streptococcus pneumoniae*

2. Based on the 2016 IDSA guidelines, which empiric antibiotic regimen is best for the likely causative pathogen(s) of K.P.'s suspected VAP?

   A. Azithromycin plus moxifloxacin
   B. Cefepime
   C. Ceftriaxone
   D. Ceftriaxone plus vancomycin

3. T.D. is a 57-year-old man admitted to the medical intensive care unit (MICU) with severe hyperosmolar hyperglycemic syndrome. A subclavian central venous catheter (CVC) is placed on his arrival at the MICU. On ICU day 4, T.D. has a temperature of 102.7°F (39.2°C) and a WBC of 17 x 10^3 cells/mm^3. The nurse notes new-onset erythema at the catheter site. After an appropriate diagnostic workup, it is decided to initiate empiric antibiotic therapy for a suspected central line–associated bloodstream infection (CLABSI). Which agent is best for empiric therapy?

   A. Cefazolin
   B. Linezolid
   C. Piperacillin/tazobactam
   D. Vancomycin

4. D.G., a 31-year-old woman, presents to the MICU with severe respiratory failure and acute respiratory distress syndrome (ARDS) requiring intubation after 48 hours of malaise, fever, and myalgias. The nasal washing sent by the emergency department (ED) for rapid diagnostic testing is positive for influenza A. The local prevalence of subtype 2009 H1N1 is high. Which agent would be most appropriate for initial treatment of D.G.'s severe influenza?

   A. Amantadine
   B. Inhaled zanamivir
   C. Intravenous zanamivir
   D. Oseltamivir

5. T.S. is a 79-year-old woman admitted to the MICU for respiratory failure and severe community-acquired pneumonia. T.S. has had a urethral catheter in place for 6 days while mechanically ventilated on fentanyl infusion and intermittent haloperidol as needed for pain and delirium, respectively. This morning, T.S. had a temperature of 101.6°F (38.7°C) and an elevation in WBC to 16 x 10^3 cells/mm^3; she is hemodynamically stable. Blood and urine cultures are sent. Urinalysis reveals significant pyuria. Which pathogen is most likely to cause a catheter-associated urinary tract infection (CAUTI) in T.S.?

   A. *Enterococcus faecalis*
   B. *Escherichia coli*
   C. *P. aeruginosa*
   D. *S. aureus*

6. K.D. is a 59-year-old man admitted to the surgical intensive care unit (SICU) after an emergency operation and partial bowel resection with primary anastomosis for mid-small bowel necrosis and perforation likely secondary to severe peripheral vascular disease. During the operation, significant peritoneal contamination with evidence of gross peritonitis was noted together with persistent hypotension and need for vasopressors. K.D. received perioperative cefazolin and metronidazole. Which empiric antibiotic regimen would be most appropriate for K.D.?

   A. Ceftriaxone and vancomycin
   B. Ciprofloxacin and metronidazole
   C. Ertapenem
   D. Piperacillin/tazobactam

7. T.M. is a 42-year-old man with chronic alcoholism who presents to the ED with severe epigastric pain and serum lipase greater than 10 times the upper limit of normal. The resident orders a computed tomography (CT) scan, which reveals necrosis affecting almost 40% of the pancreas but no abnormal fluid collections or evidence of abscess. T.M. is febrile and tachycardic, and his WBC is elevated. T.M.'s urine output is less than 0.5 mL/kg/hour, suggestive of hypovolemia. Which best describes the role of antibiotic therapy for T.M. at this time?

   A. Antibiotic therapy is not indicated.
   B. Initiate empiric antibiotic therapy for presumed sepsis and likely pancreatic infection.
   C. Initiate perioperative antibiotic therapy in preparation for pancreatic debridement.
   D. Initiate prophylactic antibiotic therapy to prevent infection of necrotic tissue.

8. J.E. is a 67-year-old woman admitted to the MICU for severe metabolic acidosis secondary to unintentional metformin overdosage. Her ICU stay has been complicated by a femoral vein CLABSI and related severe sepsis caused by pan-sensitive *E. coli*. J.E. received a 3-day course of empiric piperacillin/tazobactam, removal of her central line, and 11 days of ceftriaxone as definitive therapy with resolution of sepsis. Starting yesterday, it was noted that J.E. had nine loose bowel movements and new leukocytosis of 14,500 cells/mm^3, which suggests *Clostridioides difficile* infection (CDI). J.E. continues to tolerate enteral nutrition. Per the 2021 IDSA focused guideline update, which is the most appropriate regimen for J.E.'s suspected CDI?

   A. Fidaxomicin 200 mg per feeding tube every 12 hours
   B. Metronidazole 500 mg per feeding tube every 8 hours
   C. Metronidazole 500 mg intravenously every 8 hours
   D. Vancomycin 125 mg per feeding tube every 6 hours

9. J.S. is a 42-year-old man admitted to the SICU after an open total colectomy with ileostomy for ischemic colitis. On postoperative day 4, the surgery resident on your interdisciplinary ICU team notes moderate erythema (3 cm) and purulent drainage from the wound. The resident subsequently opens the skin portion of the wound and finds infected material just above the unaffected fascia. No systemic signs and symptoms are noted. Which intervention is most appropriate?

   A. Continue dressing changes and patient assessment.
   B. Initiate empiric vancomycin for postoperative wound infection.
   C. Initiate empiric antibiotic therapy targeted against skin and colonic flora.
   D. Initiate broad-spectrum antibiotic therapy for suspected necrotizing fasciitis.
   E.

10. T.F. is a 68-year-old man with diabetes and hypertension who presents to the ED with altered mental status and acute kidney injury. T.F. was seen at an outside hospital 5 days ago, where he tested positive for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On initial assessment, T.F. is hemodynamically stable with an oxygen saturation (SaO_2) of 87% on room air, which has worsened over the past 4 hours. T.F. now requires 5 L of high-flow nasal cannula to maintain an SaO_2 above 92%. Chest radiography is notable for bilateral opacities consistent with viral pneumonia. Initial laboratory tests indicate alanine aminotransferase 23 U/L and estimated creatinine clearance 31 mL/minute (baseline 68 mL/minute). Which agent is considered first-line therapy in hospitalized patients with coronavirus disease 2019 (COVID-19) and increasing oxygen requirement?

   A. Dexamethasone.
   B. Hydroxychloroquine.
   C. Remdesivir.
   D. Tocilizumab.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
   a. Task B: 5
2. Domain 2: Therapeutics and Patient Managment
   a. Task A: 1
   b. Task B: 12
3. Domain 3: Professional Practice
   a. Task B: 1

I. VENTILATOR-ASSOCIATED PNEUMONIA

A. Epidemiology
1. About 90% of hospital-acquired pneumonia episodes in critically ill patients occur during MV. MV is an independent risk factor for pneumonia.
2. It is estimated that 10% of all patients receiving MV develop a VAP.
3. The incidence of pneumonia increases with the duration of mechanical ventilation, with the highest risk during the first 5 days. Individual risk factors for VAP include underlying chronic lung disease, acute lung injury, aspiration, coma, trauma (e.g., chest trauma; traumatic brain injury), burns, reintubation, and overall severity of illness.
4. VAP accounts for more than 50% of antibiotic use in critically ill patients and has an attributable cost of more than $40,000 per episode.
5. VAP has an estimated all-cause mortality of 20%–50%, which varies among critically ill populations. VAP has an attributable mortality of about 13%, as seen in a recent meta-analysis.

B. Classification and Etiology
1. VAP is a distinct type of hospital-acquired pneumonia that occurs more than 48 hours after endotracheal intubation. VAP is further classified by the Centers for Disease Control and Prevention (CDC) as a ventilator-associated event and infection-related ventilator-associated complication. Updated guidelines from the IDSA for the diagnosis and management of VAP were published in 2016. (Please see Table 2 at the end of this section for summary and comparison with 2005 guidelines.)
2. VAP is usually caused by bacterial pathogens; may be monomicrobial or polymicrobial, but is rarely caused by viral or fungal pathogens.
3. The prevalence of specific bacterial pathogens varies between critically ill patient populations, geographic region, and local antibiotic usage patterns. Risk factors for multidrug-resistant organisms (MDROs) are summarized in Box 1.
4. Classification of VAP as early onset (within the first 2–4 days of hospitalization) or late onset (after 5 days or more of hospitalization) to differentiate between suspected pathogens is no longer recommended. However, longer duration (e.g., 5 days) of hospitalization before the onset of VAP is associated with nosocomial and MDRO pathogens.

Box 1. Risk Factors for MDROs Causing VAP

Prior intravenous antibiotic therapy in preceding 90 days
Acute renal replacement therapy before VAP onset
5 or more days of hospitalization before the occurrence of VAP
Septic shock at the time of VAP
ARDS preceding VAP

MDRO = multidrug-resistant organism.

C. Prevention
1. VAP is considered a reportable and preventable complication of endotracheal intubation and mechanical ventilation.
2. Data are emerging on effective prevention strategies.
3. Recommended essential practices for preventing VAP include (Infect Control Hosp Epidemiol 2022; 43:687-713):
   a. Avoid intubation and prevent reintubation if possible.
   b. Minimize sedation of ventilated patients whenever possible.

        i. Preferentially use multimodal strategies and medications other than benzodiazepines to manage agitation.
        ii. Use a protocol to minimize sedation.
        iii. Implement a ventilator liberation protocol.
    c. Maintain and improve physical conditioning, provide early exercise and mobilization.
    d. Elevate head of bed to 30–45 degrees.
    e. Maintain integrity of mechanical ventilator circuit.
    f. Provide oral care with toothbrushing but without chlorhexidine.
    g. Avoid oral care with chlorhexidine to prevent VAP in patients per recent joint recommendations by SHEA/IDSA/APIC. Meta-analyses have shown no benefit and the potential of higher mortality rates for patients receiving chlorhexidine oral care.
    h. May consider use of selective oropharynx and digestive decontamination in ICUs with low prevalence of antibiotic resistance organisms.
    i. Avoid the use of probiotics to prevent VAP in mechanically ventilated patients. While some meta-analyses found there might be a benefit, a recent large randomized controlled trial found no difference in the development of VAP in mechanically ventilated patients (Crit Care Med 2022;50:1175-86; JAMA 2021;326:1024-33).

D. Diagnosis
1. The diagnostic approach for VAP includes (1) determining whether clinical signs and symptoms are caused by pneumonia and (2) if pneumonia is present, identifying the causative pathogen(s), preferably using lower respiratory tract culture.
2. About half of mechanically ventilated patients with a clinical suggestion of pneumonia will have bacteriologically confirmed pneumonia.
3. Clinical signs and symptoms of pneumonia include new or changing infiltrate on chest radiograph and at least two of the following:
    a. Elevated WBC
    b. Fever (e.g., temperature greater than 100.4°F [38°C])
    c. Macroscopically purulent sputum production
    d. Impaired or worsening oxygenation
4. Lower respiratory tract cultures can be obtained through noninvasive or invasive techniques and reported as qualitative, semiquantitative, or quantitative.
    a. Quantitative (expressed as CFU/mL) and semiquantitative (expressed as rare/few to many) cultures using recommended diagnostic growth thresholds are more specific than qualitative cultures for identifying the causative pathogen.
    b. Noninvasive techniques: Tracheal aspirate from endotracheal or tracheostomy tube – proximal to distal sampling (depending on depth of sample) of upper airway secretions; usually semiquantitative
    c. Invasive techniques
        i. Blind, catheter-directed, or bronchoscopic BAL – Distal sampling of lung lobe/segment using saline lavage; significant quantitative growth threshold above 10,000 or 100,000 CFU/mL
        ii. Bronchoscopic protected specimen brush (PSB) – Distal sampling of specific bronchial segment; significant quantitative growth threshold above 1000 CFU/mL
    d. Rapid diagnostic tools can also be used to help in the identification of potential pathogens more speedily. Please see the Infectious Diseases II chapter for further discussion on the use of rapid diagnostic tests in the ICU.
5. According to the current IDSA guidelines, the suggested diagnostic strategy for VAP includes clinical suspicion and use of noninvasive sampling with semiquantitative cultures to diagnose VAP, rather than invasive sampling or noninvasive sampling with quantitative cultures.

   a. If an invasive strategy with quantitative cultures is used, it is suggested that antibiotics be withheld rather than continued if quantitative culture results are below the diagnostic threshold for VAP (i.e., PSB less than 1000 CFU/mL; BAL less than 10,000 CFU/mL).

E. Treatment
   1. Antibiotic therapy for VAP is empiric or definitive.
   2. Antibiotic selections should include intravenous agents able to achieve relevant pulmonary tissue concentrations related to pathogen minimum inhibitory concentration (MIC) dosed optimally using evidence-based pharmacokinetic and pharmacodynamic principles.
   3. Empiric antibiotic therapy should be initiated in patients with clinical suspicion for VAP (Table 1). Patients with septic shock should receive antibiotics within 1 hour from onset of hypotension (see Sepsis chapter).
      a. Inappropriate empiric antibiotic therapy for VAP (i.e., delay in or absence of antibiotics active against identified causative pathogen[s]) is associated with increased mortality.
      b. To decrease the likelihood of inappropriate therapy, empiric antibiotic selections should be based on:
         i. Presence of MDRO risk factor
         ii. Local VAP pathogen prevalence, particularly MRSA
         iii. Local antibiotic susceptibility patterns (i.e., ICU-specific antibiogram)
      c. All patients with suspected VAP should receive an antibiotic active against MSSA, *P. aeruginosa*, and other gram-negative bacilli.
         i. Suggest prescribing two antipseudomonal antibiotics from different classes in patients with any of the following:
            (a) MDRO risk factor
            (b) ICU antibiogram with greater than 10% of gram-negative isolates resistant to an agent being considered for monotherapy (i.e., multidrug-resistant [MDR] *P. aeruginosa*)
            (c) ICU where local antimicrobial susceptibility rates unavailable
      d. Suggest including an agent active against MRSA in patients with any of the following:
         i. MDRO risk factor
         ii. ICU MRSA prevalence greater than 10%–20% of *S. aureus*. (Note: MRSA rates vary between centers, ICUs, and populations, with general rates in U.S. hospitals greater than 20% [https://resistancemap.onehealthtrust.org/AntibioticResistance.php].)
         iii. Prevalence of MRSA is not known
      e. Combination antibiotic therapy using agents with similar bacterial spectra but different mechanisms of action may be necessary to increase the likelihood of appropriate empiric antibiotic therapy for other gram-negative pathogens.
      f. Lower respiratory tract cultures should be obtained before initiation of antibiotic therapy to increase the likelihood of identifying causative pathogen(s). Inappropriate delays in initiation of antibiotic therapy should be avoided in unstable patients (e.g., patients with septic shock).
      g. Empiric antibiotic therapy should be de-escalated to definitive therapy, depending on identified pathogen(s) and antibiotic susceptibilities. The GRACE-VAP trial, a recently published non-inferiority trial evaluated the use of Gram stain-guided restrictive antibiotic therapy in treatment of VAP. The authors found that Gram stain-guided was non-inferior to guideline-directed therapy in clinical response (76.7% vs. 71.8%), 28-day mortality (13.6% vs. 17.5%), and similar ICU-free days, ventilator-free days, and adverse events (JAMA Netw Open 2022;5:e226136).

Table 1. VAP Classifications and Recommended Empiric Antibiotic Therapy Based on 2016 IDSA VAP Guidelines

Likely Pathogens	Recommended Empiric Antibiotic(s)[a]
Patients without MDRO risk factor: Single antipseudomonal agent with 90% or greater empiric activity on local ICU antibiogram, and local MRSA prevalence is less than 10-20%	
P. aeruginosa *S. pneumoniae* *Haemophilus influenzae* α- and β-hemolytic *Streptococcus* spp. Methicillin-sensitive *S. aureus* (MSSA) Antibiotic-sensitive enteric gram-negative bacilli (GNB) (e.g., *E. coli*; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus* spp.; *Serratia* spp.)	Cefepime, imipenem, levofloxacin, meropenem, piperacillin/tazobactam
Patient without MDRO risk factor: Single antipseudomonal agent with less than 90% empiric activity on local ICU antibiogram and/or local MRSA prevalence greater than 10-20%[b]	
P. aeruginosa Methicillin-resistant *S. aureus* (MRSA) *S. pneumoniae* *Haemophilus influenzae* α- and β-hemolytic *Streptococcus* spp. Methicillin-sensitive *S. aureus* (MSSA) Antibiotic-sensitive enteric gram-negative bacilli (GNB) (e.g., *E. coli*; *Klebsiella* spp.; *Enterobacter* spp.; *Proteus* spp.; *Serratia* spp.)	Double Antipseudomonal Coverage Antipseudomonal β-lactam[c] (aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam) + Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside[d] (amikacin or tobramycin) MRSA Linezolid or vancomycin
Patients with MDRO risk factor	
P. aeruginosa Methicillin-resistant *S. aureus* (MRSA) *Acinetobacter* spp. Antibiotic-resistant enteric GNB (e.g., extended-spectrum β-lactamase [ESBL]-producing organisms) *Stenotrophomonas maltophilia*	Antipseudomonal β-lactam[c] (aztreonam, cefepime, ceftazidime, imipenem, meropenem, piperacillin/tazobactam) + Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside[d] (amikacin, gentamicin, or tobramycin) AND Linezolid or vancomycin

[a] Agents/classes are listed in alphabetic order.

[b] There may be situations in which a patient has no MDRO risk factors but may meet the recommendation to receive dual antipseudomonal therapy and/or MRSA coverage.

[c] Doripenem is no longer available in the United States. Before being discontinued, doripenem had a U.S. Food and Drug Administration (FDA) warning against use for treatment of ventilator-associated bacterial pneumonia.

[d] Guidelines suggest avoiding empiric aminoglycoside if alternative agents with activity are available. New CLSI guidance have lowered MIC breakpoints and no longer recommend the use of gentamicin in the treatment of *P. aeruginosa* infections.

4. Definitive antibiotic therapy should be focused on the causative pathogen(s) identified on lower respiratory tract culture.
    a. Pathogen-specific definitive antibiotic choices should be based on antibiotic susceptibilities and, if possible, available evidence supporting efficacy and safety in patients with VAP.
        i. MRSA: Vancomycin or linezolid; daptomycin is not indicated for pneumonia because of direct inhibition by pulmonary surfactant. Although not included in the guidelines, ceftaroline is also a potential treatment of MRSA HAP/VAP.
        ii. *P. aeruginosa*
            (a) Monotherapy with a β-lactam listed below and found to be susceptible on final culture results is recommended in immunocompetent patients not in septic shock and not at a high risk of dying. Concomitant aminoglycoside or antipseudomonal fluoroquinolone is recommended in immunocompromised patients and those in septic shock or at a high risk of dying. Combination therapy can be de-escalated to monotherapy β-lactam once septic shock resolves.
            (b) β-Lactams: Cefepime, ceftazidime (has minimal activity against MSSA and should not be used to for both *P. aeruginosa* and MSSA), piperacillin/tazobactam, imipenem, meropenem, ceftolozane-tazobactam, ceftazidime-avibactam, or cefiderocol
            (c) Aminoglycosides: Amikacin, gentamicin, or tobramycin
            (d) Fluoroquinolones: Ciprofloxacin or levofloxacin
        iii. *Acinetobacter* spp.: Sulbactam-durlobactam, ampicillin-sulbactam (sulbactam is active agent), carbapenems (eg, imipenem or meropenem), minocycline, or cefiderocol
        iv. *Stenotrophomonas maltophilia*: The combination of 2 of the following agents: sulfamethoxazole-trimethoprim, levofloxacin, minocycline, or cefiderocol. For cultures exhibiting metallo-β-lactamase, the combination of ceftazidime-avibactam and aztreonam can be used.
        v. Extended-spectrum β-lactamase (ESBL)-producing organisms: Carbapenem (e.g., ertapenem; imipenem; meropenem)
        vi. Since the 2016 IDSA guidelines, cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/cilastatin/relebactam, and sulbactam/durlobactam have been FDA approved for the treatment of VAP. These agents can be considered for certain multidrug-resistant (MDR) pathogens (e.g., ESBL; specific carbapenemases) in concert with an antimicrobial stewardship program.
        vii. In 2024, IDSA updated its guidance document in the treatment of antimicrobial-resistant gram-negative infections (*Clin Infect Dis*. 2024 Aug 7:ciae403).
    b. Duration of definitive antibiotic therapy is recommended to be 7 days for all patients rather than longer durations. Pathogen-based recommendations for duration of definitive antibiotic are no longer indicated in VAP guidelines.
        i. The PneumA trial was a pivotal noninferiority study that evaluated 8 days (7 full treatment days) versus 15 days (14 full treatment days) for duration of definitive antibiotic therapy in patients with bacteriologically diagnosed VAP. The primary noninferiority outcome was VAP recurrence. All patients included in the study received appropriate empiric antibiotic therapy (JAMA 2003;290:2588-98). Major study findings were:
            (a) Definitive antibiotic therapy for 8 days was noninferior to 15 days in patients with VAP not caused by non–lactose-fermenting gram-negative bacilli (e.g., *P. aeruginosa*).
            (b) Patients with VAP caused by non–lactose-fermenting gram-negative bacilli in the 8-day group more often had VAP recurrence. This was primarily seen in patients with *P. aeruginosa*, but also included other lactose-non-fermenters (e.g., *Acinetobacter, Stenotrophomonas*, and *Burkholderia* spp.).

        - (c) The rate of MDR pathogens during a recurrent VAP episode was higher in patients in the 15-day group.
      - ii. Two meta-analyses that included the results of the PneumA trial suggest limited benefit of prolonged duration of definitive antibiotic therapy for treating VAP (Chest 2013;144:1759-67; Cochrane Database Syst Rev 2015;8:CD007577). Synopsis includes:
        - (a) Any increase in VAP recurrence rate is small;
        - (b) Mortality and clinical cure do not appear to be affected by shorter durations;
        - (c) Evidence for recurrence from subgroup analyses has important limitations.
      - iii. Guidelines acknowledge that situations may exist in which shorter or longer durations of definitive antibiotic therapy may be indicated, depending on the rate of clinical and radiologic improvement. A single-center, retrospective study suggested that patients with "possible VAP" who had minimal and stable ventilator settings at diagnosis are appropriate for short-course therapy (i.e., 1-3 days) (Clin Infect Dis 2017;64:870-6). However, application of these findings is limited, given that only 39% of short-course patients had an identified pathogen on tracheal aspirate or BAL culture, bringing into question the likelihood of confirmed pneumonia.
      - iv. The iDIAPASON Trial was a randomized, controlled, open-label trial that compared 8 versus 15 days of antibiotic therapy solely for the treatment of Pseudomonas aeruginosa ventillator-associated pneumonia (PA-VAP). The primary noninferiority endpoint was a composite outcome of death and PA-VAP recurrence during the ICU stay until day 90. Duration of therapy was counted from the time of effective antibiotic therapy (Intensive Care Med 2022;48:841-9). Major study findings were the following:
        - (a) Short duration was not associated with an increased mortality, longer duration of mechanical ventilation, or length of ICU stay.
        - (b) While not significant, there was a trend toward higher proportion of recurrence in the 8 days of therapy compared with 15 days (17% vs. 9.2%; confidence interval [CI], –0.5% –16.8%).

5. Response to antibiotic therapy should be assessed serially using clinical signs and symptoms of infection (e.g., oxygenation requirements, blood pressure, WBC, temperature) and status of VAP-related organ dysfunction.
   - a. Lack of response in signs and symptoms of VAP beyond treatment day 3 necessitates reassessment of diagnosis, causative pathogen(s), antibiotic regimen, and presence of pneumonia-related complications (e.g., ARDS).
   - b. Patients thought to have persistent VAP should undergo repeat lower respiratory tract culture and receive empiric antibiotic therapy considering previous pathogen(s) and antibiotic exposure.

Table 2. Summary of Key Changes in 2016 IDSA VAP Guidelines

Characteristic	2005 Guidelines	2016 Guidelines
Methodology	Expert opinion based on level of evidence ranging from Level I (high) to III (low)	GRADE criteria to identify "recommended" (strong) or "suggested" (weak) guidance based on level of evidence categories "very low," "low," "moderate," and "high quality"
Diagnosis	Clinical strategy or bacteriologic strategy	Suggest clinical suspicion with noninvasive sampling and semiquantitative cultures If invasive sampling is used, suggest that antibiotics be withheld rather than continued if quantitative culture results are below the diagnostic threshold for VAP

Table 2. Summary of Key Changes in 2016 IDS VAP Guidelines *(continued)*

Characteristic	2005 Guidelines	2016 Guidelines
Classification	Early onset or late onset	No longer differentiate VAP episodes based on time from hospital admission Emphasis on local risk assessment for *P. aeruginosa* and MRSA occurring early in hospitalization
MDRO Risk Factors	• Antibiotic therapy in preceding 90 days • Chronic dialysis within 30 days • Current hospitalization of 5 days or more • Home chronic wound care • Home infusion therapy • Hospitalization in the preceding 90 days • Immunosuppressive disease and/or therapy • Known contact or colonization with MDROs • Residence in a nursing home or extended-care facility	• Prior intravenous antibiotic therapy in preceding 90 days • Acute renal replacement therapy before VAP onset • 5 or more days of hospitalization before the occurrence of VAP • Septic shock at the time of VAP • ARDS preceding VAP
Empiric Therapy	Categorized based on early onset or late onset and presence of MDRO risk factor • Early onset without MDRO risk factor: no antipseudomonal or MRSA coverage • Late onset or early onset with MDRO risk factor: dual antipseudomonal and MRSA coverage	Recommend coverage for MSSA, *P. aeruginosa*, and other gram-negative bacilli in all empiric regimens. Suggest including an agent active against MRSA if any of the following: • MDRO risk factor for antimicrobial resistance • ICU MRSA prevalence greater than 10%-20% of all S. aureus • Prevalence of MRSA is not known Suggest prescribing dual antipseudomonal antibiotics from different classes if any of the following: • MDRO risk factor for antimicrobial resistance • ICUs with greater than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy • ICU where local antimicrobial susceptibility rates unavailable
Aminoglycosides	No specific recommendation	Suggest avoiding if alternative agents with adequate gram-negative activity are available
Colistin	No specific recommendation	Suggest avoiding if alternative agents with adequate gram-negative activity are available
Duration of Definitive Therapy	In patients who received appropriate empiric antibiotic therapy: • Non–lactose-fermenting Gram negative bacilli: 14 days • All other pathogens: 7 days	Recommend 7 days rather than longer durations regardless of pathogen Suggest using procalcitonin plus clinical criteria to guide discontinuation of antibiotic therapy, rather than clinical criteria alone

Patient Cases

1. C.T. is a 48-year-old man sustaining a 40% total body surface area burn to his left side with likely inhalational injury requiring mechanical ventilation. C.T. has been in the ICU for 7 days. Overnight, C.T. had a temperature of 102.1°F (39°C), a WBC of 18 x 10^3 cells/mm^3, and an increase in macroscopically purulent sputum production; C.T. is hemodynamically stable with no signs of new-onset organ dysfunction. C.T.'s chest radiograph is difficult to assess, given his inhalational injury. The respiratory therapist was asked by the fellow to do a catheter-directed BAL for suspected VAP. The culture was sent to the microbiology laboratory. Which would be best to do at this point?
   A. Initiate broad-spectrum empiric antibiotic therapy for suspected MDR VAP.
   B. Await 1–2 days for Gram stain results to determine empiric antibiotic regimen.
   C. Await preliminary quantitative culture results before initiating empiric antibiotic therapy.
   D. Send blood and urine cultures, and await their results before initiating empiric antibiotic therapy.

2. C.P. is a 67-year-old woman with a medical history significant for chronic obstructive pulmonary disease (COPD), type 2 diabetes, and coronary artery disease. She is readmitted to the ICU with respiratory failure requiring intubation secondary to severe COPD. C.P. had a 10-day hospitalization 12 days ago, during which time she received intravenous azithromycin for a COPD exacerbation. On day 4 of this readmission, a worsening infiltrate is in the left lower lung base with increased sputum production from admission, maximum temperature is 101.9°F (38.8°C), and there is worsening oxygenation, despite previous improvement in initial COPD exacerbation. The patient is thought to have clinical VAP, and a semiquantitative tracheal aspirate is sent to identify causative pathogen(s). The local ICU prevalence of MRSA is 30%, and the most active β-lactam antibiotic against *P. aeruginosa* on the antibiogram has 80% activity. Which empiric antibiotic regimen is best for this patient?
   A. Azithromycin plus moxifloxacin.
   B. Cefepime plus tobramycin, and vancomycin.
   C. Ceftriaxone plus azithromycin.
   D. Linezolid plus tobramycin.

3. K.L., a 37-year-old man who presents after a motorcycle collision, has sustained several orthopedic and chest injuries. K.L. has been mechanically ventilated for 8 days, during which time he was given a diagnosis of VAP caused by *Klebsiella pneumoniae*. K.L. received appropriate empiric antibiotic therapy and has improved oxygenation, decreased WBC temperature curve. Which would be the best duration of definitive antibiotic therapy for K.L.'s VAP?
   A. 24 hours after resolution of clinical signs and symptoms.
   B. 7 days.
   C. 10 days.
   D. 14 days.

II. CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTIONS

A. Epidemiology, definition, etiology, and prevention for CLABSI are discussed in the Infectious Diseases II chapter.

B. Diagnosis
   1. Clinical signs and symptoms of infection have poor sensitivity and specificity. Fever is the most sensitive clinical finding, whereas inflammation or purulence at the insertion site is the most specific.
   2. If a CLABSI is suspected, paired blood cultures drawn from the catheter (at least one hub/port) and from a peripheral vein should be obtained. The individual bottles should be appropriately marked through the culture-reporting period.
      a. If a blood culture cannot be drawn from a peripheral vein, it is recommended that at least two blood cultures be obtained through different catheter hubs/ports.
      b. Blood cultures positive for *S. aureus*, coagulase-negative staphylococci, or *Candida* spp. that are not attributable to another source should increase the suggestion of CLABSI.
      c. Blood cultures should be obtained before initiation of antimicrobial therapy, as appropriate.
   3. A definitive diagnosis of CLABSI requires positive percutaneous blood culture results with positive culture of same pathogen from the catheter tip or catheter-drawn cultures. Please see the Infections Diseases II chapter for further discussion on the pathway for regulatory reporting of CLABSI.

C. Treatment
   1. Catheter removal should be considered in all patients with a confirmed CLABSI. If a CVC is still necessary, a different anatomic site should be used. Changing to a new catheter at the same site using a guidewire or catheter introducer should be avoided.
   2. Antimicrobial therapy for CLABSI is empiric or definitive.
   3. Inappropriate empiric antimicrobial therapy is associated with increased mortality, including bacterial and fungal etiologies.
      a. Empiric antimicrobial therapy should minimally include an agent active against methicillin-resistant coagulase-negative (e.g., methicillin-resistant *S. epidermidis* [MRSE]) or coagulase-positive (e.g., MRSA) staphylococci. Vancomycin or daptomycin are preferred; linezolid should not be used for empiric management of CLABSI.
      b. Pathogen-specific risk factors, documented colonization, and previous antimicrobial exposure should be considered when choosing empiric antimicrobial therapy.
         i. Patients at risk of MDROs should receive combination therapy against gram-negative bacilli using agents from separate antibiotic classes.
         ii. Patients at high risk of candidemia include those receiving TPN, those with prolonged use of broad-spectrum antibiotics, those with hematologic malignancy, those who have received a bone marrow or solid-organ transplant, those with femoral catheterization, and those with colonization because of *Candida* spp at multiple sites. A Candida score may be used to help predict risk, but it is primarily validated in surgical ICU patients.
            (a) Use of an echinocandin (eg, anidulafungin, caspofungin, or micafungin) should be considered for patients at risk of candidemia.
            (b) Fluconazole is reasonable in patients without recent exposure to an -azole in the previous 6 months and in health care settings with a low prevalence of non-susceptible species.
      c. Local antimicrobial activity should be considered to increase the probability of appropriate therapy.
      d. Empiric antimicrobial therapy should be de-escalated, depending on the identified pathogen(s) and related antimicrobial susceptibility. Antimicrobial therapy should be discontinued if a CLABSI is not evident and there are no other sources of infection.
   4. Definitive management and antimicrobial therapy should be based on whether the CLABSI is complicated or uncomplicated (more common than complicated) and the identified pathogen(s). Ongoing clinical trials may provide guidance to the optimal duration of antibiotic therapy for CLABSI and non–central line-associated bacteremia (BMJ Open 2020;10:e038300).
      a. The duration of antimicrobial therapy should be based on the first day of negative blood culture.

b. Complicated CLABSI
  i. Endocarditis; immunosuppression (*S. aureus* only); diabetes (*S. aureus* only); chronic intravascular hardware; osteomyelitis; positive blood cultures greater than 72 hours from initiation of appropriate therapy; septic thrombus; thrombophlebitis
  ii. Remove catheter.
  iii. Treat with pathogen-targeted antimicrobial therapy for 4–6 weeks; 6–8 weeks for osteomyelitis.

c. Uncomplicated CLABSI
  i. Coagulase-negative staphylococci
    (a) Consider catheter removal. If catheter is retained, consider antibiotic lock therapy in addition to systemic antibiotic therapy for 10–14 days.
    (b) Treat with systemic antibiotic therapy for 5–7 days if the catheter is removed.
  ii. *S. aureus*
    (a) Remove catheter.
    (b) Treat with systemic antibiotic therapy for a minimum of 14 days.
      (1) Methicillin-sensitive *S. aureus* (MSSA) – Penicillinase-resistant penicillin (e.g., nafcillin); first-generation cephalosporin (e.g., cefazolin) (Note: Vancomycin has been shown inferior to β-lactam therapy for MSSA.)
      (2) MRSA – Vancomycin; daptomycin or linezolid; sulfamethoxazole/trimethoprim
    (c) Patients with catheter tip bacterial growth but negative blood cultures should receive antibiotic therapy for 5–7 days with close monitoring for signs and symptoms of ongoing infection and consideration for repeat blood cultures.
  iii. *Enterococcus* spp.
    (a) Remove catheter.
    (b) Treat with systemic antibiotic therapy for 7–14 days.
  iv. Gram-negative bacilli
    (a) Remove catheter.
    (b) Treat with systemic antibiotic therapy for 7–14 days.
  v. *Candida* spp.
    (a) Remove catheter.
    (b) Treat with systemic antifungal therapy for at least 14 days.
  vi. Antibiotic lock therapy in the treatment of CLABSI should be used primarily for catheter salvage. In the event antibiotic therapy cannot be used in this situation, then recommendation is to administer antibiotics through the colonized catheter.

Patient Cases

4. T.W. is a 47-year-old woman admitted to the MICU with respiratory failure secondary to severe 2009 H1N1 influenza infection. T.W., who requires intubation and mechanical ventilation, is given a diagnosis of septic shock associated with influenza and a secondary MSSA pneumonia. An internal jugular vein CVC was placed in the ED during acute resuscitation. T.W. continues to require a CVC. Although her hypotension and fever resolved 72 hours post-admission, she has a new temperature of 101.7°F (38.7°C) with worsening leukocytosis on ICU day 5; there is no change on her chest radiograph. Which action would be best to take next?

  A. Initiate broad-spectrum antibiotic therapy for a new sepsis episode.
  B. Perform bronchoscopic BAL for suspected VAP.
  C. Remove CVC.
  D. Send two sets of blood cultures, one from the catheter and one from a peripheral blood sample.

Patient Cases *(continued)*

Questions 5 and 6 pertain to the following case.
F.P. is a 29-year-old man admitted to the MICU from another hospital with severe, alcohol-induced, sterile acute pancreatitis. During his 5-day stay at the outside hospital, he had multiple organ failure, including respiratory failure requiring tracheostomy. A right internal jugular CVC was placed on the patient's admission to the outside hospital. On MICU day 3, F.P. has a maximum temperature of 102°F (38.9°C). Two sets of blood cultures are obtained; the right internal jugular catheter is removed and the tip sent for culture.

5. Which regimen would be best to consider for empiric management of a suspected CLABSI?
   A. Daptomycin and ceftriaxone.
   B. Fluconazole.
   C. Linezolid and cefepime.
   D. Vancomycin, cefepime, and tobramycin.

6. F.P. is found to have *K. pneumoniae* CLABSI and receives appropriate empiric antibiotic therapy. He has had a good clinical response with no persistence of bacteremia. Which represents the best duration of F.P.'s definitive antibiotic therapy for CLABSI?
   A. 5 days.
   B. 14 days.
   C. 21 days.
   D. 4 weeks.

III. CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

A. Epidemiology, definitions, etiology, and prevention for CAUTIs are discussed in the Infectious Diseases II chapter.

B. Diagnosis
   1. Although clinical signs and symptoms are the mainstay for differentiating CAUTIs from catheter-associated asymptomatic bacteruria, they are not specific for CAUTI. These include fever, rigors, altered mental status, malaise, or lethargy with no other identified cause. Presence of flank pain, costovertebral angle tenderness, acute hematuria, and pelvic discomfort may be more specific, but these are difficult to assess in many critically ill patients.
   2. Urine culture should be obtained in all critically ill patients with signs and symptoms of CAUTI. Sampling should be done through the catheter port using aseptic technique. Catheters in place for longer than 2 weeks should be replaced and a urine sample obtained from the port of the newly placed catheter. Samples from the catheter collection system (e.g., catheter bag) should be avoided because of the potential for colonization.
   3. Urinalysis should be obtained in patients with a suspected CAUTI. Pyuria without signs and symptoms does not indicate CAUTI; however, the absence of pyuria in a symptomatic patient suggests a diagnosis other than CAUTI.

C. Treatment
1. A urinary culture should be obtained before initiation of antimicrobial therapy.
2. If an indwelling catheter has been in place for longer than 2 weeks, the catheter should be removed or, if still indicated, replaced to hasten resolution of symptoms.
3. Similar to other health care–acquired infections, empiric antimicrobial therapy should be based on local pathogen prevalence, pathogen-specific risk factors (e.g., MDRO risk factors), previously identified pathogens, previous antimicrobial exposure, and local antibiotic susceptibility.
4. Empiric antimicrobial therapy should be de-escalated according to the identified pathogen(s) and respective antimicrobial susceptibility on final urine culture results. Empiric antimicrobial therapy should be discontinued in patients without CAUTI or other sources of infection.
5. Definitive antimicrobial therapy should be based on final antimicrobial susceptibility results and presence of concomitant infection(s). Catheter irrigation (i.e., bladder washings) is not recommended.
6. Shorter duration of antimicrobial therapy should be considered depending on clinical response. Regardless of catheter removal, duration of antimicrobial therapy should be 7 days for patients with resolution of signs and symptoms within 72 hours of appropriate antimicrobial therapy and up to 14 days in patients with resolution after 72 hours.
7. Patients with persistent signs and symptoms of CAUTI should receive a urologic workup to assess for abscess or other causes of relapse.

Patient Case

Questions 7 and 8 pertain to the following case.
P.H. is a 67-year-old woman admitted from a long-term care facility to the MICU for respiratory failure secondary to severe pneumonia. P.H. is initiated on vancomycin and levofloxacin and has a urethral catheter placed in the emergency department. On ICU day 6, P.H. has a new fever with a temperature of 101.9°F (38.9°C) and an elevated WBC to 18 x 10^3 cells/mm^3, despite an initial clinical response to pneumonia therapy. Blood and urine cultures are sent. Urinalysis reveals many bacteria and greater than 10 white blood cells/mm3.

7. Which intervention is most appropriate in P.H.?
   A. Await final culture results before changing the current antibiotic regimen.
   B. Continue pneumonia therapy for an extended treatment duration.
   C. Initiate empiric antibiotic therapy for a suspected catheter-associated urinary tract infection (CAUTI).
   D. Insert a new urinary catheter and resend a urinalysis to confirm CAUTI.

8. P.H.'s fever and leukocytosis resolved in less than 48 hours, and antibiotics were narrowed according to the final susceptibilities report. Which best depicts how long the ICU team should treat P.H.'s CAUTI?
   A. 5 days of effective therapy.
   B. 7 days of effective therapy.
   C. 10 days of effective therapy.
   D. 14 days of effective therapy.

IV. COMPLICATED INTRA-ABDOMINAL INFECTION

A. Epidemiology
   1. Complicated intra-abdominal infection spans prehospital and in-hospital dispositions and a variety of pathogenic processes involving several organ systems.
   2. The incidence of complicated intra-abdominal infection is difficult to estimate, given the breadth of illness. Appendicitis is the most prevalent cause of complicated intra-abdominal infection. Recent controlled trials and large international observational sepsis studies report abdominal infection as the second or third most common source of sepsis, accounting for 21% of sepsis and 30% of septic shock cases.
   3. Complicated intra-abdominal infection is the second most common cause of mortality in critically ill patients. Crude mortality for primary intra-abdominal infection is almost 30%, whereas rates exceed 50% in patients with secondary intra-abdominal infection. Those presenting with sepsis caused by intra-abdominal infection have crude mortality above 40%.

B. Definitions
   1. The IDSA and Surgical Infection Society (SIS) jointly published guidelines for the management of intra-abdominal infection in 2010. In 2017, the Surgical Infection Society updated these guidelines, including management for complicated intra-abdominal infection, which are reflected throughout this section. As an additional resource, an international group published recommendations in 2021 on a global approach to diagnosis and management of specific intra-abdominal infections (World J Emerg Surg 2021;16:49).
   2. A complicated intra-abdominal infection is defined as infection that extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. These infections usually arise from spillage of viscus-related fluid and flora into the peritoneal cavity, causing inflammation and injury to the peritoneal membrane. Retroperitoneal infections also are possible, but these are related to the individual retroperitoneal organ rather than the peritoneum.
   3. Peritonitis is described as primary, secondary, and tertiary.
      a. Primary peritonitis, or spontaneous bacterial peritonitis, is peritonitis related to bacterial translocation of proximal small bowel overgrowth and not peritoneal disruption or organ perforation. Primary peritonitis is generally diffuse in nature.
      b. Secondary peritonitis is caused by leakage of intraluminal fluid and microorganisms secondary to macro- or microperforation of the GI tract. Secondary peritonitis can be diffuse or localized to an organ, depending on the extent of peritoneal involvement. Causes of secondary peritonitis include direct trauma, ischemia, thrombosis, ulceration, malignancy, and anastomotic leak.
      c. Tertiary peritonitis is peritonitis that persists or recurs at least 48 hours after the management of primary or secondary peritonitis. Tertiary peritonitis can represent a new intra-abdominal process or host, anatomic, or therapeutic failure of treatment of primary or secondary peritonitis.

C. Etiology
   1. Pathogens associated with complicated intra-abdominal infections and peritonitis are influenced by type/cause of peritonitis, MDRO risk factors, previous antibiotic exposure, and patient-specific colonization. Patients having health care–associated intra-abdominal infections more often tend to have antibiotic-resistant, nosocomial pathogens compared with patients having community-acquired infection.
   2. Primary peritonitis also known as spontaneous bacterial peritonitis, is usually monomicrobial and associated with translocation of organisms across the diaphragm or proximal small bowel. The most prevalent organisms include *S. pneumoniae*, *E. coli*, and *Klebsiella* spp.
   3. Secondary peritonitis is typically polymicrobial related to the origin of GI tract leakage.

   a. Esophageal, gastric, and duodenal secretions are usually sterile or with limited inocula of gram-positive bacteria and *Candida* spp.
   b. Proximal small bowel is densely populated with aerobic gram-negative bacilli including *E. coli*, *Klebsiella* spp., *Proteus* spp., and Enterobacter spp., as well as populations of aerobic gram-positive bacteria such as *S. aureus*, streptococci, and enterococci.
   c. The distal small bowel and the large bowel are populated with proximal small bowel flora in addition to anaerobic gram-negative and gram-positive organisms, including *Bacteroides fragilis* and *Clostridioides* spp. (usually non–*C. difficile*).
4. Tertiary peritonitis includes core organisms of primary and secondary peritonitis further compounded by the influence of management strategies, including malnutrition, anatomic disruption, and antimicrobial therapy.

D. Diagnosis
1. The diagnosis of complicated intra-abdominal infection relies on assessment of clinical signs and symptoms, differentiation from other causes of infection, and radiographic evaluation.
2. Rapid-onset abdominal pain and tenderness with signs of peritoneal irritation on physical examination are the most common presenting signs and symptoms. Additional symptoms of anorexia, abdominal distention, nausea, or vomiting, with or without fever, tachycardia, or tachypnea. These are often difficult to assess in critically ill patients; therefore, intra-abdominal infection should be considered in patients with unexplained new-onset organ dysfunction and sepsis.
3. Radiographic evaluation is commonly performed using abdominal radiographs, ultrasonography, and CT, including contrast CT to assess for vascular thrombosis. Contrast studies of postoperative drains or fistulae may also help assess anastomotic integrity.
4. Culture of intra-abdominal fluid (e.g., ascitic fluid in patients with cirrhosis; intraoperative culture of abscess fluid) associated with the primary source should be obtained in moderately to severely ill patients. Gram stain results should be used to help guide empiric antimicrobial therapy. Pathogens identified on final culture should guide definitive antimicrobial therapy.

E. Management and Treatment
1. Resuscitation for hemodynamic instability should be initiated and managed according to the Surviving Sepsis Campaign guidelines.
2. Achieving primary source control of ongoing peritoneal contamination by operative diversion or resection is recommended for patients with diffuse peritonitis. Patients with focal peritonitis should undergo percutaneous abscess and fluid drainage.
3. Empiric antimicrobial therapy should be initiated in patients thought to have complicated intra-abdominal infections.
   a. Empiric antimicrobial regimens should be based on the source/location of intra-abdominal infection, community-acquired or health care–associated disposition of infection, severity of infection, local pathogen trends and susceptibilities, MDRO risk factors (e.g., hospitalization for greater than 48 hours during current admission or in the previous 90 days; recent broad-spectrum antimicrobial therapy; infection developing greater than 48 hours after initial source control; home wound care or dialysis within preceding 90 days), and patient-specific colonization patterns.
   b. Individual antimicrobial agents should be dosed according to available pharmacokinetic and pharmacodynamic principles to optimize efficacy and limit toxicity.

c. Community-acquired, mild to moderate severity, low risk for treatment failure
  i. Routine culture is not recommended.
  ii. Empiric antibiotic therapy should include agents active against aerobic and facultative enteric gram-negative bacilli and enteric streptococci. Obligate anaerobic therapy should be initiated in patients with distal small bowel, appendiceal, or colonic sources. Concerns with emergence of antibiotic resistance may limit the utility of narrower-spectrum agents (e.g., cefazolin; cefoxitin). Anti-enterococcal and antipseudomonal therapies are not recommended.
    (a) Either ceftriaxone or cefotaxime in combination with metronidazole (generally considered first line)
    (b) Cefuroxime plus metronidazole
    (c) Ertapenem
    (d) Moxifloxacin alone; levofloxacin or ciprofloxacin plus metronidazole for patients with severe β-lactam allergies
    (e) Tigecycline
      (1) No longer guideline recommended for empiric use, but can be considered for definitive treatment.
      (2) Pooled results from approval trials across all infections suggests increased mortality in patients treated with tigecycline versus active comparator regimens. The cause of this increase has not been established.
      (3) FDA-approved label warns that the increase in all-cause mortality should be considered when selecting among treatment options.

d. Community acquired, high risk for treatment failure defined as two or more of the following risk factors: Severe physiologic disturbance (e.g., septic shock); advanced age; immunocompromised state; diffuse peritonitis; delay in, or high likelihood of failure to achieve primary source control
  i. Routine culture of intra-abdominal fluid is recommended as available.
  ii. Empiric antimicrobial therapy should be broadened to include MDROs, enterococci, and obligate anaerobes. Agents active against MRSA are not recommended empirically. Although fluoroquinolones are recommended, emergence of resistant *E. coli* and *P. aeruginosa* is a concern.
    (a) Broad-spectrum carbapenem (e.g., imipenem, meropenem)
    (b) Either cefepime or ceftazidime in combination with metronidazole (may need additional anti-enterococcal agent)
    (c) Either ciprofloxacin or levofloxacin in combination with metronidazole (may need additional anti-enterococcal agent)
    (d) Piperacillin/tazobactam (or cefepime/ceftazidime) would not be appropriate if an ESBL infection

e. Health care associated
  i. Routine culture of intra-abdominal fluid is recommended as available.
  ii. Broad-spectrum empiric antimicrobial therapy should include coverage for MDR Gram negative bacilli (e.g., *P. aeruginosa*) and obligate anaerobes. Depending on empiric antibiotic susceptibility rates (i.e., local antibiogram), combination therapy against aerobic gram-negative bacilli with aminoglycoside, or, if MDROs are prevalent, ceftolozane-tazobactam and/or polymyxin.
    (a) Broad-spectrum carbapenem (e.g., imipenem, meropenem with or without anti-enterococcal therapy)
    (b) Either cefepime or ceftazidime (second line agent) in combination with metronidazole.
    (c) Piperacillin/tazobactam

      iii. Anti-enterococcal therapy should be considered in patients with recent exposure to broad-spectrum antimicrobial therapy, septic shock, postoperative infections, and those documented colonization with enterococci.
      iv. Anti-MRSA therapy should be considered in patients known to be colonized with MRSA or with MDRO risk factors, including advanced age, co-morbid medical conditions, previous hospitalization or surgery, and significant recent exposure to antibiotic agents.
      v. Antifungal therapy should be added to the regimen of patients with yeast on Gram stain, recent evidence of heavy colonization, surgically treated pancreatitis, prolonged broad-spectrum antibiotic therapy, or critically ill patients with an upper gastrointestinal source. Fluconazole is the drug of choice for fluconazole-susceptible strains. Echinocandins should be used first line in critically ill patients until final culture results are available.
      vi. Empiric antimicrobial therapy should be de-escalated to final culture results and related antimicrobial susceptibilities.

4. New guidance from the SIS regarding the duration of antimicrobial therapy in patients with intra-abdominal infections (*Surg Infect (Larchmt*). 2024;25(6):419-435):
   a. The authors recommend limiting antimicrobial therapy to 4 days after achieving source control, given the results of the STOP-IT trial (*N Engl J Med*. 2015;372(21):1996-2005), including patients at high risk with sepsis, or those at increased risk of complications from diabetes, obesity, or higher-severity illness (grade 1-B recommendations).
   b. The authors go on to recommend limiting antimicrobial therapy to 8 days in critically ill patients after achieving source control of intra-abdominal infections (grade 2-B).
      i. This recommendation came from the limited data of critically ill patients included in the STOP-IT as well as other studies.
      ii. This recommendation is based on a single open-label randomized controlled trial, a systematic review meta-analysis, and a retrospective cohort trial that compared durations of 8 vs 15 days or 5 vs 10 days.
5. Considerations for short-term prophylactic courses no longer than 24 hours include:
   a. Acute gastric or jejunal perforation in absence of malignancy or acid-reducing pharmacotherapy with adequate source control within 24 hours
   b. Traumatic or iatrogenic bowel injuries repaired within 12 hours of injury
   c. Acute appendicitis without perforation or abscess

Patient Cases

9. D.L. is a 69-year-old woman admitted from home to the SICU with severe acute abdominal pain in the left lower quadrant. An abdominal CT reveals free air in the peritoneal cavity and evidence of distal ischemic colitis. D.L. is taken urgently to the operating room, where she is noted to have gross contamination from distal colonic perforation with marked peritonitis. After a partial colectomy and abdominal washout, she is admitted to the SICU for continued resuscitation for septic shock. Which empiric antibiotic regimen would be most appropriate for D.L.?
   A. Ceftriaxone and vancomycin.
   B. Ciprofloxacin and metronidazole.
   C. Ertapenem.
   D. Piperacillin/tazobactam.

Questions 10 and 11 pertain to the following case.
K.D. is a 58-year-old man with severe peripheral vascular disease admitted from home to the SICU with severe acute abdominal pain in the left lower quadrant. An emergency abdominal CT reveals free air in the peritoneal cavity and evidence of distal small bowel ischemia. K.D. is taken emergently to the operating room for an exploratory laparotomy, where he is noted to have gross peritoneal contamination with marked peritonitis from a small bowel perforation. Intraoperative cultures were sent and are pending. After primary repair of the distal small bowel and abdominal washout, K.D. returns to the SICU for continued resuscitation for septic shock.

10. Which empiric antibiotic regimen would be most appropriate for K.D.?
   A. Meropenem and linezolid.
   B. Ertapenem.
   C. Ciprofloxacin and vancomycin.
   D. Cefazolin, metronidazole, and fluconazole.

11. Given that K.D. is critically ill after achieving source control following his procedure and the team is asking about duration of antimicrobial therapy, which antimicrobial duration limit after source control would be best to recommend to the team?
   A. 5 days.
   B. 8 days.
   C. 10 days.
   D. 15 day.

V. ACUTE PANCREATITIS

A. Epidemiology
   1. Acute pancreatitis is responsible for more than 200,000 acute care admissions annually in the United States.

2. About 20% –30% of acute pancreatitis episodes are severe, have evidence of pancreatic necrosis, and are associated with local and systemic complications (e.g., multiple organ failure). An Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 8 or higher and a Ranson's criteria score of 3 or greater, together with clinical presentation, have been used historically to categorize patients as having severe acute pancreatitis. The more recent revised Atlanta classification categorizes severe acute pancreatitis as the presence of single or multiple organ failure for 48 hours or more, whereas the Determinant-Based Criteria (DBC) classification system defines it as persistent organ failure or infected pancreatic or peripancreatic necrosis. The DBC adds a category of critical acute pancreatitis for patients with persistent organ failure and infected necrosis.
3. Between 30% and 78% of patients with necrotizing pancreatitis will have concomitant organ failure, with the highest incidence in patients having infected necrosis. Pancreatitis-associated systemic sequelae and organ failure includes:
    a. Systemic inflammatory response syndrome (SIRS)
    b. Hypovolemic shock
    c. Hypoxemia secondary to ARDS
    d. Acute kidney injury
    e. Gastrointestinal (GI) bleeding
    f. Disseminated intravascular coagulation and severe metabolic disturbances can also occur.
4. Although most pancreatic necrosis is sterile and does not require treatment with antimicrobials, about one-third of patients with necrotizing pancreatitis will have infected necrosis.
5. Overall, crude mortality for acute pancreatitis is 2%–9%; however, mortality rates for necrotizing and infected necrotic pancreatitis with organ failure are as high as 44% and 62%, respectively.

B. Pathophysiology
1. Pancreatitis is a result of glandular autodigestion from excessive ductal and tissue exposure to amylase, lipase, and protease caused by trypsin-related hyperstimulation, macro-ductal blockade, or micro-ductal blockade.
2. The pathophysiology of acute pancreatitis can be organized into three phases:
    a. Excessive activation or decreased inactivation of trypsin leading to activation of pancreatic exocrine enzymes
    b. Local inflammatory and immune response to pancreatic injury
    c. Systemic inflammatory and immune response, including SIRS, hypovolemia, and ARDS
3. Common causes of acute pancreatitis include biliary obstruction (e.g., gallstones), direct toxicity (e.g., alcohol), trauma, surgery/biliary procedures, hypertriglyceridemia, and drugs.

C. Definitions
1. Severe pancreatitis is defined as pancreatitis associated with organ failure that persists for more than 48 hours. Hypovolemia may increase the risk of pancreatic necrosis and intestinal ischemia because of tissue hypoperfusion.
2. Pancreatic necrosis is evidenced on CT scan as diffuse or focal areas of nonviable pancreatic tissue often associated with peripancreatic fat necrosis. In general, greater than 30% of the pancreas should be affected. Infected necrosis is defined as the presence of pathogenic microorganisms in the necrotic tissue. The presence of retroperitoneal gas on CT scan may indicate infected pancreatitis in patients with severe acute pancreatitis. The timing of infected necrosis varies, but infected necrosis usually peaks 2–4 weeks from the onset of acute pancreatitis.
3. Pancreatic pseudocyst is a non-epithelialized wall containing pancreatic excretions caused by acute or chronic pancreatitis or pancreatic trauma. Pseudocysts are usually sterile.
4. Pancreatic abscess is an infected pseudocyst or liquefaction of pancreatic necrosis that becomes infected.

5. Additional late complications of peripancreatic necrosis include secondary pancreatic infection of previously acute necrotic collections during the first 4 weeks after presentation and walled-off necrosis, which may lead to pancreatic abscess that matures after 4 weeks or more.

D. Diagnosis
   1. The diagnosis of acute pancreatitis requires two of the following three features:
      a. Acute and constant epigastric or right upper quadrant abdominal pain with or without nausea and vomiting;
      b. Serum amylase and/or lipase greater than 3 times the upper limit of normal; and
      c. Characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging.
   2. Patients with severe pancreatitis may present with SIRS, hypovolemia, and new-onset organ failure, including hypotension.

E. Management and Treatment
   1. Management of severe acute pancreatitis includes acute pain management, fluid resuscitation, supportive care of systemic complications and organ failure, and nutrition support. Surgical debridement of infected necrosis or drainage of pancreatic abscess should be considered.
      a. Initial fluid management should be goal-directed titration of isotonic, crystalloid intravenous fluids using clinical and biochemical targets of perfusion. Results of the ERICA Trial support moderate fluid volumes over more aggressive resuscitation (N Engl J Med 2022;387:989-1000).
      b. Patients should receive nutrition within 24 hours. Patients unable to eat orally should receive enteral nutrition by nasogastric or nasojejunal access over parenteral nutrition.
      c. Patients should be monitored and approriately treated for acute pain during acute pancreatitis. Refer to chapter on management of pain in the ICU.
   2. Antibiotic therapy for acute pancreatitis is considered empiric, definitive, or prophylactic.
      a. Empiric antibiotic therapy is indicated in patients with suspected or confirmed infected necrosis or pancreatic abscess. The diagnosis of infected pancreatitis is difficult because the clinical picture may mimic other infectious complications because of the likelihood of systemic signs of inflammation.
         i. Patients with suspected infected necrosis or pancreatic abscess should undergo radiographically (e.g., ultrasonography, CT) guided drainage with culture of recovered material/fluid. Common organisms associated with infected necrosis or pancreatic abscess include:
            (a) *E. coli*
            (b) *Klebsiella* spp.
            (c) *Enterobacter* spp.
            (d) *Proteus* spp.
            (e) Streptococci
         ii. The antibiotics of choice include:
            (a) Piperacillin-tazobactam or broad-spectrum carbapenems (e.g., imipenem; meropenem)
            (b) Third-or-fourth generation cephalosporin plus metronidazole (limit use to patients with serious β-lactam allergies)
            (c) Fluoroquinolone plus metronidazole
         iii. Antifungal therapy should be added to antibiotic therapy if yeast is identified on culture Gram stain. Fluconazole is recommended unless there is a high suspicion for fluconazole-resistant fungi.
         iv. Empiric antibiotics should be discontinued if pancreatic culture is negative, indicating sterile pancreatitis. Patients with persistent SIRS should undergo repeat imaging and drainage of identified abscess or fluid.

   v. If infection is confirmed, antibiotic therapy should be de-escalated toward the identified pathogen(s) according to antibiotic susceptibility.
   vi. Definitive antibiotic therapy for confirmed infection should be continued for up to 14 days.
  b. Prophylactic antimicrobial therapy in patients with sterile necrotizing pancreatitis is controversial. Although small pilot investigations suggest benefit, a large, noninferiority, placebo-controlled trial suggested no benefit with prophylactic meropenem. Current recommendations do not support routine use of prophylactic antibiotic or antifungal therapy in patients with sterile necrotizing pancreatitis. (Gastroenterology 2018;154:1096-101; Am J Gastroenterol 2013;108:1400-15; World J Emerg Surg 2019;14:27)

3. Ongoing assessment of resolution of SIRS, trending of procalcitonin, and pancreatitis-associated organ failure is imperative. Serial assessment of serum amylase or lipase has limited value over clinical assessment and physical examination. Elevation of serum amylase or lipase for several weeks, however, should heighten concern for persistent pancreatic/peripancreatic inflammation, blockage of the pancreatic duct, or development of a pseudocyst.

Patient Cases

12. R.P. is a 43-year-old man with a history of chronic alcohol abuse who presents to the emergency department from home with acute, severe epigastric abdominal pain; heart rate 142 beats/minute; MAP 62 mm Hg; WBC 24 x 10^3 cells/mm^3; and serum lipase 1527 U/L. R.P. receives 3 L of normal saline intravenously over 60 minutes. An immediate abdominal CT scan is remarkable for significant pancreatic edema and greater than 30% necrosis of the pancreas. There is no evidence of an acute fluid collection. Which antimicrobial regimen would be most appropriate for R.P.?
    A. Ceftriaxone and vancomycin.
    B. Ciprofloxacin and metronidazole.
    C. Meropenem.
    D. None; prophylactic antibiotic therapy is not indicated in acute pancreatitis.

13. T.J. is a 27-year-old man who is admitted to the MICU from an outside hospital with alcohol-induced acute pancreatitis and associated respiratory failure, SIRS, and blood pressure 100/55 mm Hg. Admission abdominal CT shows severe pancreatitis with about 30% necrosis and a large focal fluid collection requiring guided drainage. A fluid sample is sent for a Gram stain, which reveals many gram-negative rods and yeast. Which antimicrobial regimen would best be initiated in T.J.?
    A. None – low suspicion for infected pancreatitis.
    B. Ciprofloxacin and metronidazole.
    C. Imipenem.
    D. Meropenem and fluconazole.

VI. *CLOSTRIDIOIDES DIFFICILE* INFECTION

A. Epidemiology
  1. *C. difficile* (also known as *Clostridioides difficile*) is a spore-forming, anaerobic, gram-positive bacillus. Stool carriage of *C. difficile* has been found in up to 26% of acute care patients.

2. *C. difficile* is transmitted person to person through the fecal-oral route. The capability to become dormant in spores increases the potential for environmental spread.
3. *C. difficile* is pathogenic through the production and expression of two primary toxins, *C. difficile* toxin A (TcdA) and *C. difficile* toxin B (TcdB). North America has seen a recent emergence of strains with increased virulence (e.g., BI/NAP1 strain) through increased production of toxins A and B, production of additional toxins, and enhanced sporification.
4. CDI is responsible for almost 30% of antibiotic-associated diarrhea and is the most common cause of infectious diarrhea in health care settings. The estimated incidence of CDI is 3–10 cases per 10,000 patient-days. Community-acquired CDI has increased in prevalence.
5. The clinical manifestations of CDI range from asymptomatic carrier to CDI spanning mild or moderate diarrhea to fulminant and sometimes fatal pseudomembranous colitis, toxic megacolon, or colonic perforation. Post-colectomy small bowel enteritis and rectal pouchitis related to CDI have been reported. Additional complications of severe CDI include:
    a. SIRS
    b. Hypovolemia
    c. Electrolyte disturbances
    d. Sepsis and septic shock
    e. Multiple organ failure
6. CDI is associated with medical costs greater than $3 billion per year.
7. Attributable mortality from CDI is estimated to be below 10%. However, crude mortality is as high as 75% in patients presenting with septic shock, colonic perforation, or toxic megacolon. Subtotal colectomy in patients with a severe CDI is associated with an in-hospital mortality rate of up to 42%.

B. Definitions

1. CDI is defined as the presence of symptoms (e.g., diarrhea) and a stool test result positive for *C. difficile* toxin, toxigenic *C. difficile* (e.g., DNA amplification detecting toxin-coding genes), or pseudomembranous colitis on colonoscopic examination. The most recent guidelines for CDI diagnosis and management include those from the American College of Gastroenterology in 2021 (Kelly CR, et al. Am J Gastroenterol 2021;116:1124 -47), IDSA/SHEA guidelines from 2017, and a focused update from IDSA/SHEA in 2021 related to management of CDI. The ACG 2021 guidelines are updated from the 2013 version to harmonize CDI severity categories with IDSA/SHEA while expanding a focus on diagnostic methods and management of patients with concomitant chronic inflammatory bowel disease.
2. Severe CDI according to expert-based guidelines is defined as stated earlier, plus:
    a. IDSA 2017 and 2021; ACG 2021
        i. WBC 15 x 10^3 cells/mm^3 or greater and
        ii. Serum creatinine (SCr) 1.5 times or greater than the premorbid level
3. Fulminant (IDSA 2017 and 2021; ACG 2021) CDI is defined as:
    a. Severe CDI plus one of the following:
        i. Hypotension or evidence of shock
        ii. Ileus
        iii. Megacolon
4. Recurrence is defined as the relapse of a recent infection or a reinfection after definitive therapy.
5. Additional categorizations of CDI are used for infection control surveillance and institutional/ICU quality review. These are related to the locations of *C. difficile* acquisition (e.g., community acquired or health care associated) and onset of symptoms (e.g., community onset vs. health care onset).

C. Risk Factors
   1. Antibiotic therapy is the most important risk factor.
      a. All antibiotic classes have been associated with CDI.
      b. Highest-risk (listed by decreasing risk) antibiotic classes include clindamycin, fluoroquinolones, cephalosporins/carbapenems, and penicillins.
   2. Gastric acid–suppressing pharmacotherapy, including proton pump inhibitors and histamine-2 receptor antagonists
   3. Age older than 65 years
   4. Duration of hospitalization
   5. Cancer chemotherapy
   6. GI surgery
   7. Previous CDI

D. Prevention – There are two global strategies to prevent CDI:
   1. Decrease the risk of acquiring *C. difficile*.
      a. Staff, patient, family, caregiver education
      b. Hand hygiene to remove *C. difficile* spores through non–alcohol-based handwashing using soap or chlorhexidine gluconate and water
      c. Contact isolation, including full-barrier precautions (gown and gloves), single-occupancy room, and the cohorting of patients with a CDI
      d. Limit reuse or between-patient sharing, and terminal clean patient care–related equipment (e.g., digital thermometers, point-of-care blood glucose machines, dietary trays, intravenous infusion pumps) and rooms (previous antibiotic use by the previous bed occupant may increase the risk of CDI in the current occupying patient).
      e. Environmental decontamination using bleach-containing cleaning solution
   2. Avoid or address reversible risk factors.
      a. Limit overuse of, and discontinue unnecessary, antibiotic therapy.
      b. Decrease duration of hospital stay.
      c. Discontinue unnecessary gastric acid–reducing pharmacotherapy.

E. Diagnosis
   1. Diagnosis of CDI is based on clinical and laboratory findings.
   2. Clinical findings include presence of diarrhea, defined as passage of three or more unformed stools within 24 consecutive hours.
      a. Rarely, a symptomatic patient will present with ileus and colonic distension with minimal or no diarrhea.
      b. Patients with cecal CDI or right-sided CDI colitis may have formed stools.
   3. Laboratory findings include stool sample positive for toxigenic *C. difficile*, *C. difficile* toxin, or colonoscopic or histopathologic findings showing pseudomembranous colitis. Available strategies for detecting toxin-producing *C. difficile* include:
      a. Testing for *C. difficile* should only be performed on unformed stool unless patients have ileus. Identifying the ideal testing strategy remains difficult. Institution-specific decisions for which test(s) to use should be evidence based and collaborative across interested parties. Moreover, institutions should consider creating local interdisciplinary guidelines for *C. difficile* testing to avoid positive results in colonized patients without infection.
      b. Stool culture with detection of a toxigenic isolate through identification of neutralizable toxin activity is considered the gold standard test. However, this process could take up to 9 days, limiting its clinical utility.

   c. Enzyme immunoassay (EIA) tests for *C. difficile* toxins A and B are rapid and widely available; however, poor sensitivity may limit their utility. Obtaining serial samples has been used to increase sensitivity. Sensitivity may also be increased using a two-step process with initial EIA to detect the *C. difficile* antigen glutamate dehydrogenase and a follow-up stool culture with detection of the toxigenic isolate.
   d. PCR testing is rapid, sensitive, and specific. Widespread availability may be limited.
   e. The nucleic acid amplification test (NAAT) involves an illumigene *C. difficile* assay, which uses loop-mediated isothermal DNA amplification to detect a specific genetic region responsible for coding toxins A and B. It is recommended to only test patients with symptoms of CDI using NAAT because of risk of potential false-positive results.
4. Recommended laboratory diagnostic pathways differ regarding whether an institution-specific protocol for stool sample quality based on CDI likelihood is predefined. Briefly, the absence of predefined criteria requires a multistep laboratory process that includes a toxin test (e.g., NAAT plus toxin assay) rather than a NAAT alone. In contrast, the presence of predefined criteria for stool quality and clinical presentation suggestive of CDI permits the use of NAAT alone or a multistep process over a strategy using a toxin assay alone.
5. The same diagnostic criteria are used for recurrent CDI.

F. Management and Treatment
   1. Removal of potential cause(s), as appropriate (e.g., discontinuation of associated antibiotic therapy)
   2. Assessment of disease severity (mild or moderate vs. severe) and whether episode is initial or recurrent
   3. Evaluation of need for surgical intervention
      a. Subtotal colectomy with rectal preservation should be considered for severely ill patients.
      b. Alternative colon-sparing operative surgical strategies have been described.
   4. Antibiotic therapy targeted against *C. difficile* (Table 3)
      a. Samples for diagnostic testing for *C. difficile* should be obtained before empiric antibiotic therapy is initiated. Initiation of empiric antibiotic therapy before final test results should be based on clinical assessment.
      b. Antibiotic choices and respective routes of administration should be based on severity of CDI and ability to achieve relevant intraluminal antibiotic concentrations relative to CDI. Special considerations include:
         i. Fidaxomicin, an oral, limited-bioavailability macrolide antibiotic, is indicated for treatment of CDI. The 2021 IDSA/SHEA focused guideline update recommends (conditional recommendation; moderate certainty of evidence) fidaxomicin as first-line therapy for first episode, non-fulminant CDI when access to fidaxomicin is not inhibited by limited resources. This recommendation is supported by systematic review and meta-analysis of four studies noting increased sustained response to therapy at 4 weeks with fidaxomicin compared to oral/enteral vancomycin. Initial cure, all-cause mortality, and drug adverse events were similar between fidaxomicin and vancomycin. Data supporting fidaxomicin use in critically ill patients are limited to small representative sample sizes and retrospective or observational studies.
         ii. Oral or enteral vancomycin continues to be an alternative for an initial episode of CDI when access to and availability of fidaxomicin is limited. The optimal enteral vancomycin dosage in critically ill patients is unknown. Although ACG and IDSA guidelines recommend enteral vancomycin dosages of 125 mg four times daily for uncomplicated/nonfulminant CDI (Table 3), some practices consider dosages of 250 mg four times daily if there is lack of response or if there is concern for subclinical GI dysmotility (e.g., incomplete enteral nutrition tolerance, elevated gastric residuals, abdominal distention) (Int J Antimicrob Agents 2013;42:553-8; Clin Infect Dis 2015;61:934-41).

- iii. Metronidazole is primarily only recommended in addition to oral vancomycin for the treatment of severe-complicated/fulminant CDI. The IDSA guidelines indicate that metronidazole is a valid treatment option for "initial episode, non-severe" CDI when fidaxomicin and oral vancomycin are unavailable or for patients with limited access to resources to attain these medications. Use of metronidazole as first-line therapy in patients with an initial episode of mild-moderate CDI is also supported by the World Society of Emergency Surgery.
- iv. For enema volumes in patients requiring rectal instillation of vancomycin, location of CDI-affected area(s) and risk of colonic perforation should be considered. Patients receiving vancomycin enemas may need a cuffed rectal delivery device/tube to facilitate retention.
- v. Patients with CDI-related colitis and proximal colonic diversion (i.e., no continuity with oral or gastric route) may require rectal instillation of vancomycin enema.
- vi. Fecal transplantation has improved outcomes compared with oral vancomycin in noncritically ill patients with recurrent CDI. Logistical challenges with product availability or stool sample collection, fecal delivery and administration, and risk of colonization with pathogenic organisms (e.g., E. coli) should be considered.
- vii. There are no definitive recommendations for duration of CDI antibiotic therapy or prevention of recurrence when non-CDI antibiotic therapy is continued concurrently.

c. Response to therapy should be assessed by evaluating clinical signs and symptoms, including resolution of diarrhea, laboratory abnormalities, sepsis, and related organ failure. Results of stool testing for *C. difficile* in patients with resolution of disease do not predict recurrence.

Table 3. Treatment Options for *Clostridioides difficile* Infection

Clinical Definition	ACG 2013	IDSA/SHEA 2018	IDSA/SHEA 2021 Focused Update	ACG 2021
Initial episode, nonsevere	Metronidazole 500 mg PO/NG/FT TID for 10 days	Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days —OR— Fidaxomicin 200 mg BID for 10 days *Alternative*: Metronidazole 500 mg PO/NG/FT TID for 10–14 days (delayed response)	Fidaxomicin 200 mg PO/NG/FT BID for 10 days *Alternative:* Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days *Alternative for nonsevere infection if above agents are unavailable*: Metronidazole 500 mg PO/NG/FT TID for 10–14 days (delayed response)	Fidaxomicin 200 mg PO/NG/FT BID for 10 days (strong recommendation; moderate-quality evidence) —OR— Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days (strong recommendation; low-quality evidence)
Initial episode, severe	Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days	Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days —OR— Fidaxomicin 200 mg BID for 10 days		Vancomycin 125 mg PO/NG/FT 4 times daily for 10 days (strong recommendation; low-quality evidence) —OR— Fidaxomicin 200 mg PO/enteral BID for 10 days (conditional recommendation; very low-quality evidence)
Initial episode, severe complicated (ACG)/ fulminant (IDSA)	Vancomycin 125 mg PO/NG/FT 4 times daily + metronidazole 500 mg IV TID *Ileus*: Vancomycin 500 mg PO/NG/FT and per rectum (NS 500 mL) + metronidazole 500 mg IV TID	Vancomycin 500 mg PO/NG/FT 4 times daily + metronidazole 500 mg IV TID *Ileus*: Add rectal vancomycin 500 mg/ NS 100 mL instilled for 1 hr 4 times daily	Vancomycin 500 mg PO/NG/FT 4 times daily + metronidazole 500 mg IV TID *Ileus*: Add rectal vancomycin 500 mg/ NS 100 mL instilled for 1 hr 4 times daily	Same as IDSA/SHEA 2021 Surgery: Suggest total colectomy with end ileostomy and stapled rectal stump or diverting loop ileostomy with colonic lavage and intraluminal vancomycin

Table 3. Treatment Options for *Clostridioides difficile* Infection *(continued)*

Clinical Definition	ACG 2013	IDSA/SHEA 2018	IDSA/SHEA 2021 Focused Update	ACG 2021
First recurrence	Same regimen as used for initial episode, unless severe; if severe, vancomycin should be used	Vancomycin 125 mg 4 times daily for 10 days if metronidazole was used for initial episode —OR— Prolonged tapered and pulsed vancomycin regimen if standard regimen was used for initial episode; for example: 125 mg 4 times daily for 10–14 days, BID for 1 wk, once daily for 1 wk, then every 2 or 3 days for 2–8 wk —OR— Fidaxomicin 200 mg PO/NG/FT BID for 10 days if vancomycin was used for initial episode	Fidaxomicin 200 mg PO/NG/FT BID for 10 days—OR—BID for 5 days, then once every other day for 20 days *Alternative*: Vancomycin PO in tapered and pulsed regimen —OR— Vancomycin 125 mg given 4 times daily PO for 10 days *Adjunctive therapy*: Bezlotoxumab 10 mg/kg IV once during administration of above antibiotics	Recommend fidaxomicin for first recurrence after initial course of vancomycin or metronidazole (conditional recommendation, moderate-quality evidence) Suggest tapering/pulsed dose vancomycin first recurrence after initial course of fidaxomicin, vancomycin, or metronidazole (strong recommendation, very low-quality evidence) Suggest bezlotoxumab for high risk of recurrence (conditional recommendation, moderate-quality evidence)

Table 3. Treatment Options for *Clostridioides difficile* Infection *(continued)*

Clinical Definition	ACG 2013	IDSA/SHEA 2018	IDSA/SHEA 2021 Focused Update	ACG 2021
Second recurrence	Vancomycin PO, then 28-day dosage taper	Vancomycin in tapered and pulsed regimen —OR— Vancomycin 125 mg PO 4 times daily for 10 days, then rifaximin 400 mg TID for 20 days —OR— Fidaxomicin 200 mg PO/NG/FT BID for 10 days —OR— Fecal microbiota transplantation	Fidaxomicin 200 mg PO/NG/FT BID for 10 days—OR—BID for 5 days, then once every other day for 20 days —OR— Vancomycin PO in tapered and pulsed regimen —OR— Vancomycin 125 mg 4 times daily PO for 10 days, then rifaximin 400 mg TID for 20 days —OR— Fecal microbiota transplantation (preferably after 3 antibiotic courses are attempted and completed) *Adjunctive therapy*: Bezlotoxumab 10 mg/kg IV once during administration of above antibiotics	Recommend fecal microbiota transplant (FMT) to prevent further recurrences (strong recommendation, moderate-quality evidence) Suggest bezlotoxumab for high risk of recurrence (conditional recommendation, moderate-quality evidence)

ACG = American College of Gastroenterology; BID = twice daily; FT = feeding tube; IDSA = Infectious Diseases Society of America; IV = intravenously; NS = normal saline; PO = orally; SHEA = Society for Healthcare Epidemiology of America; TID = 3 times daily.

Information from: Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clin Inf Dis 2021. Available at www.idsociety.org/globalassets/idsa/practice-guidelines/cdi-2021-focused-update.pdf. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66:987-94. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections. Am J Gastroenterol 2013;108:478–98.; Kelly CR, Fischer M, Allegretti JP, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections, Am J Gastroenterol 2021; 116: 1124-1147.

Patient Cases

14. K.L. is a 57-year-old man admitted to the MICU with diffuse abdominal pain, temperature 101.9°F (38.8°C), WBC 27 x 10^3 cells/mm^3, heart rate 125 beats/minute, and mean arterial pressure 57 mm Hg. An abdominal CT scan reveals a large amount of intestinal air, suggestive of ileus and moderate transverse and sigmoid colonic inflammation. On review of the patient's history, it is learned that K.L. recently completed a 4-week course of broad-spectrum antibiotic therapy for a postoperative osteomyelitis after repair of right comminuted femur fracture, increasing the suggestion of CDI. Which regimen would be best for empiric management of a suspected CDI in K.L.?

    A. Metronidazole 500 mg intravenously every 8 hours.
    B. Vancomycin 500 mg orally/by nasogastric tube/feeding tube four times daily, metronidazole 500 mg intravenously every 8 hours, and intracolonic vancomycin 500 mg instilled every 8 hours.
    C. Metronidazole 500 mg orally or by nasogastric tube every 8 hours and vancomycin 250 mg orally or by nasogastric tube every 6 hours.
    D. Vancomycin 250 mg orally or by nasogastric tube every 6 hours.

Questions 15 and 16 pertain to the following case.
E.A. is a 79-year-old man admitted to the MICU for severe pneumonia. On day 5 of treatment with broad-spectrum antibiotic therapy despite negative culture, E.A. is noted to have several liquid bowel movements requiring a rectal pouch (around 1.6 L of stool in past 24 hours), a low-grade fever, elevation of WBC at 27 x 10^3 cells/mm^3, heart rate 124 beats/minute, MAP 67 mm Hg, lactate 1.6 mmol/L, and SCr 1.5 mg/dL. A stool sample is sent for a suspected *C. difficile* infection (CDI).

15. Which regimen would be the best empiric management of a suspected CDI in E.A.?

    A. Metronidazole 500 mg intravenously every 8 hours and intracolonic vancomycin 500 mg instilled every 8 hours.
    B. Metronidazole 500 mg intravenously every 8 hours.
    C. Metronidazole 500 mg orally or by nasogastric tube every 8 hours and vancomycin 125 mg orally or by nasogastric tube every 6 hours.
    D. Vancomycin 125 mg orally or by nasogastric tube every 6 hours.

16. E.A. is initiated on vancomycin because fidaxomicin is unavailable for his CDI. Which treatment duration would be best for E.A.?

    A. 7 days.
    B. 10 days.
    C. 14 days.
    D. 4 weeks.

VII. WOUND INFECTION

A. The epidemiology, definitions, etiology, and prevention for postoperative wound infections are discussed in the Infectious Diseases II chapter.

B. Diagnosis
  1. Postoperative wound infections most commonly occur 48 hours after the procedure. Fever in the first 48 hours is usually idiopathic or from noninfectious causes.
  2. Wounds should be physically examined serially until healed. Purulent material should be collected aseptically and sent for Gram stain and culture. Cultures in patients with suspected deep tissue infections should be obtained from deep tissues with concomitant blood cultures.
  3. Signs and symptoms of superficial incisional postoperative wound infection include:
     a. Purulent incisional drainage
     b. Local pain or tenderness, swelling, and erythema after the incision is opened
     c. Positive culture of purulent drainage
  4. Necrotizing fasciitis should be suspected if the following are present:
     a. Severe pain that seems disproportional to the appearance of the wound
     b. Failure to respond to initial antibiotic therapy
     c. Hard, wooden feel of the subcutaneous tissue, often extending beyond the area of affected skin
     d. Crepitus on physical examination or radiographic (radiograph, CT scan) finding, indicating gas in subcutaneous tissues
     e. Skin necrosis or ecchymoses
     f. Sepsis or septic shock

C. Management and Treatment
  1. Opening of the incision, evacuation of the infected material, and continued dressing changes are the foundation of treatment for confirmed postoperative wound infections.
  2. Antibiotic therapy targeted against likely pathogens should be initiated in patients with systemic signs and symptoms or suspected deep tissue infection.
  3. Superficial incisional infection
     a. Erythema and induration less than 5 cm and minimal systemic signs of infection (no fever, no leukocytosis, and tachycardia):
        i. Serial dressing changes
        ii. No antibiotic therapy necessary
        iii. Continue to assess wound for resolution or progression.
     b. Erythema and induration greater than 5 cm, fever, leukocytosis, and tachycardia:
        i. Open suture line.
        ii. Initiate empiric antibiotic therapy targeted against operative site–related suspected pathogens. Examples include:
           (a) Extremity, head, neck, or trunk site: Cefazolin or vancomycin if MRSA suspected
           (b) GI, genitalia, or perineum site: Cephalosporin or levofloxacin plus metronidazole; ertapenem
        iii. Adjust antibiotics according to culture results. Continue for up to 48 hours or until infection is resolved.
        iv. Serial dressing changes
        v. Continue to assess wound for resolution or progression.
  4. Necrotizing fasciitis
     a. Surgical debridement of necrotic tissue serially (i.e., every 24–48 hours) until no further need for debridement

- b. Antibiotic therapy is empiric or definitive.
    - i. Empiric antibiotic therapy should be initiated as early as possible.
    - ii. Polymicrobial infection should be suspected, with empiric therapy that is active against aerobic and anaerobic gram-positive and gram-negative pathogens
        - (a) Vancomycin or linezolid, plus:
        - (b) Piperacillin/tazobactam, broad-spectrum carbapenem, or cefepime plus metronidazole
        - (c) If linezolid is not initially chosen, adding clindamycin to the treatment regimen can be considered.
            - (1) Both demonstrate potential decrease in pathogenic toxin and cytokine production if *Streptococcus pyogenes* is suspected.
            - (2) Both seem to be clinically effective, with limited data supporting the benefit of one over the other (*Open Forum Infect Dis*. 2023;10(6):ofad258).
    - iii. Empiric antibiotic therapy should be de-escalated according to final culture results.
    - iv. Definitive antibiotic therapy should be based on final culture results and antibiotic susceptibility. Infection caused by *S. pyogenes* should be treated with an active β-lactam or vancomycin (in severe penicillin allergy) plus clindamycin for up to 72 hours or while the patient requires surgical debridement. Use of intravenous immunoglobulin (IVIG) is controversial. Limited evidence suggests a shorter time to no further need for debridement but no effect on mortality.
    - v. Antibiotic therapy should be continued until surgical debridement is no longer necessary and until resolution of infection-related signs and symptoms.

5. Organ or space infection: See individual chapters, sections, or guidelines for managing organ/space-specific infection (e.g., pancreatitis, intra-abdominal infection; genitourinary tract).

Patient Case

Questions 17 and 18 pertain to the following case.
R.J. is a 57-year-old man admitted to the SICU after a bowel resection following an acute bowel obstruction. On postoperative day 3, R.J. has worsening tachycardia and decreased urinary output together with a maximum temperature of 102.9°F (39.4°C) and a WBC of 18.2 x 10^3 cells/mm^3. R.J. reports worsening pain around his large abdominal surgical wound despite minimal erythema. On opening a few sutures of the wound, pus is expressed on examination, and crepitus is noted in the area surrounding the wound. R.J. is emergently taken to the operating room for exploration and is noted to require significant debridement of necrotic subcutaneous tissue, including the involved fascia. R.J.'s wound is left open with a temporary gauze dressing.

17. Which empiric antimicrobial regimen is most appropriate for R.J.?
    - A. Ceftaroline and vancomycin.
    - B. Clindamycin, penicillin G, and vancomycin.
    - C. Piperacillin/tazobactam, clindamycin, and vancomycin.
    - D. Clindamycin and linezolid.

18. Intraoperative tissue culture from the first debridement of R.J.'s wound shows many gram-positive cocci in chains and moderate non–lactose-fermenting gram-negative bacilli. R.J. is to undergo serial intraoperative debridements of necrotic tissue. Given the concern for *S. pyogenes* from the Gram stain, which pharmacotherapeutic intervention would be most appropriate for treatment of R.J.'s necrotizing fasciitis?
    - A. Add synergistic gentamicin.
    - B. Continue or initiate adjunctive clindamycin for toxin production.
    - C. Ensure vancomycin is part of the regimen for concerns of *S. pyogenes* resistance.
    - D. Give intravenous immunoglobulin (IVIG).

VIII. INFLUENZA

A. Epidemiology
   1. Influenza is a seasonal viral illness affecting all ages and associated with significant morbidity and mortality. Seasonal patterns in the United States vary from year to year. For example, the 2008–2009 influenza season started in November 2008 and waned by April 2009, but then, because of influenza A H1N1 (2009 H1N1), it resurged in May 2009, peaking in mid-October 2009 and persisting to April 2010. The 2023-2024 season started to significantly increase in October 2023 before peaking in December 2023.
   2. According to the CDC, it is estimated that 400,000–900,000 patients a year in the United States are hospitalized with influenza-related illness. During the previous 2020–2021 season, the reported overall rate (cumulative rate per 100,000 population) of hospitalization for laboratory-confirmed influenza was 0.8, notably lower than previous seasons (67 for 2019–2020 season). However, the rate increased during the 2021–2022 season to 17.3, which is still notably lower compared with rates prior to the SARS-CoV-2 pandemic. The average weekly rate of hospitalization from influenza was 0.1, with a peak of 8.9 during the 2023-2024 season. Age-related rates for adult hospitalizations were 50.4 for those 65 years of age and older, 16.0 for 50–64 years of age, and 9.1 for 18–49 years of age. The rate of ICU admission among those hospitalized was 14.3%, compared to the the five seasons from 2015–2020 (range 15%–19%).
   3. Risk factors for severe influenza requiring hospitalization include chronic respiratory or metabolic illness, immunosuppression (disease or pharmacotherapy), pregnancy, and age older than 65 years. In 2009, re-emergence of the high-virulence strain influenza A H1N1 (pandemic 2009 H1N1) caused significant morbidity and mortality in young adults and other groups considered at a lower risk of severe influenza. The pandemic 2009 H1N1 strain continues to be tracked and varies significantly from year-to-year. In 2023-2024, the 2009 H1N1 was responsible for approximately 49.5% of reported influenza cases in the United States.
   4. The most common complications of severe influenza include hypoxemic respiratory failure, bacterial pneumonia, and ARDS. Concomitant sepsis, septic shock, multiple organ failure, encephalopathy, and rhabdomyolysis also are associated with severe influenza.
   5. Among all causes of deaths in the United States, pneumonia and influenza have surpassed the epidemic threshold since 2009, with rates close to 10% during the peak of influenza seasons. Severe influenza caused by the 2009 H1N1 strain has been associated with crude mortality rates of 15%–53%.

B. Etiology
   1. Influenza is caused by the RNA viruses influenza A, B, or C, which usually spread through droplet transmission. Influenza A and B viruses are the predominant causes of clinically significant illness. Influenza virus subtypes are described by surface proteins hemagglutinin (H) and neuraminidase (N).
   2. According to the CDC, influenza A has been the most prevalent cause of influenza since 2009, with 2009 H1N1 and H3N2 being the most prevalent influenza A subtypes. Influenza B prevalence has varied during the same period, but it remains an important cause of illness. Overall for 2023-2024, influenza A was isolated in 77.3% of cases. The most common specified influenza strain isolated was influenza A H1N1 at 49.5% of all influenza A and influenza B subtyped specimens.
   3. Influenza viruses can cause a broad range of respiratory tract infections, ranging from mild to moderate upper respiratory tract infections to severe pneumonia. Influenza infection has been associated with acute viremia.

C. Prevention
   1. Annual vaccination remains the primary tool for influenza prevention.
   2. In-hospital and ICU outbreaks of influenza can contribute to viral transmission and associated sequelae.

3. Institutions should begin implementing influenza screening and infection control measures when influenza viruses are confirmed to be in the local community.
4. The CDC recommends the implementation of droplet precautions for hospitalized patients with suspected or confirmed influenza; further, these precautions are recommended for 7 days after illness onset or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer.

D. Diagnosis
1. Patients with influenza may present with fever, myalgias, headache, malaise, dry cough, pharyngitis, and rhinorrhea. Fever and myalgias generally last 3–5 days, whereas malaise and respiratory symptoms may last 2 weeks or more. Patients with severe influenza may present with hypoxemic respiratory failure and sepsis.
2. Clinical signs and symptoms of influenza are nonspecific. To confirm the diagnosis of influenza, sampling of the upper respiratory tract using nasal washing or nasopharyngeal swab or lower respiratory tract within 5 days of illness is preferred. Diagnostic tests obtained beyond 5 days may have false-negative results.
3. Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays.
   a. Viral culture and reverse transcription polymerase chain reaction (RT-PCR) are the most sensitive and are the only tests able to identify individual influenza subtypes. These tests can be performed using nasopharyngeal swab or respiratory tract culture (e.g., sputum, BAL).
   b. Rapid diagnostic tests of nasopharyngeal swab or nasal wash have high specificity (90%–95%) (i.e., low false-positive rate and rapid turnaround), promoting these tests as first line for general diagnosis. Depending on the rapid diagnostic assay used, differentiation between influenza A and influenza B is possible, although further subtype identification is not available with these tests. Because of poor sensitivity, negative rapid diagnostic tests should be followed up with viral culture or RT-PCR.
4. Case definitions for influenza surveillance are suspected, probable, or confirmed based on patient presentation and laboratory assessment.
   a. Suspected – Mild to severe influenzalike illness within reasonable seasonal threshold.
   b. Probable – Mild to severe influenzalike illness within reasonable seasonal threshold or after recent contact with person with probable or confirmed influenza infection and not otherwise explained.
   c. Confirmed – Mild to severe influenzalike illness with confirmatory laboratory tests indicating presence of influenza A or B.

E. Management and Treatment
1. Management of critically ill patients with influenza includes treatment of primary influenza infection, secondary bacterial infection(s), and related noninfectious complications (e.g., respiratory failure, ARDS, prolonged mechanical ventilation, multiple organ failure). Management of common bacterial infections and noninfectious complications is described in other chapters.
   a. Diagnostic tests for influenza should be obtained and empiric antiviral treatment of influenza initiated during seasonal outbreaks in critically ill patients presenting with acute febrile and respiratory illness consistent with influenza. Severely ill patients with influenza may present with hypothermia similar to other populations with sepsis. Accompanying severe hypoxemic respiratory failure should heighten the concern for influenza.
   b. Antiviral treatment (Table 4) should be initiated within 48 hours from onset of symptoms. Hospitalized patients receiving antiviral therapy after 48 hours from symptom onset may benefit. The CDC recommends that treatment be initiated even 5 days after symptoms in critically ill patients.

c. Neuraminidase inhibitors continue to be the mainstay of antiviral therapy for recent influenza A and B strains. These agents inhibit viral neuraminidase, decreasing the release of post-replication viral particles (virions) from infected cells, limiting spread to additional tissues. Neuraminidase inhibition may also suppress the initiation of infection after acute inoculation.
    i. Oseltamivir phosphate is an oral (capsule, powder for suspension) ethyl ester prodrug converted through hepatic ester hydrolysis to the active form oseltamivir carboxylate. Oseltamivir can be administered to critically ill patients by orogastric or nasogastric tube. An intravenous formulation of oseltamivir has been tested in early clinical trials. Oseltamivir is the drug of choice for hospitalized patients with severe influenza.
    ii. Zanamivir is available on the market as an orally inhaled drug delivered by a Diskhaler device. Intravenous zanamivir was once available for patients with severe influenza through clinical trial participation or emergency investigational new drug through the manufacturer. However, this program has been discontinued for countries outside the European Union (internal communication).
    iii. Peramivir is an intravenous neuraminidase inhibitor with activity against influenza A and B. Peramivir was approved in December 2014 for use in patients 18 years or older with acute uncomplicated influenza. Peramivir is administered as a single 15-minute intravenous infusion. Data are limited for peramivir in critically ill patients.

d. Adamantanes inhibit the replication of influenza A viruses by preventing viral assembly. Adamantanes also interfere with the function of the transmembrane domain of the viral M2 protein, preventing release of viral particles into host cells.

e. Baloxavir is an endonuclease inhibitor approved by the FDA in 2018 for the management of uncomplicated influenza in individuals older than 12 years. Baloxavir inhibits endonuclease of influenza virus A and B strains, limiting the activity of the polymerase acidic protein responsible for viral gene transcription and virus replication. Data are limited on its safety and efficacy in patients with severe influenza.

f. A recent multicenter study together with a systematic review and meta-analysis showed that the use of corticosteroids in the treatment of influenza was associated with increased hospital mortality in adult patients (*Ann Intensive Care.* 2020;10(1):26; *Crit Care Med.* 2020;48(2):e98-e106).

g. Susceptibility of influenza to available antiviral agents varies from year to year and between strains and subtypes. Local surveillance of susceptibility patterns at the beginning and throughout a respective season is imperative to provide appropriate therapy.
    i. In the past three seasons, close to 100% of tested influenza A (2009 H1N1 and H3) and B viruses were susceptible to oseltamivir, peramivir, and zanamivir.

ii. High levels of resistance to the adamantanes (amantadine and rimantadine) have persisted among circulating influenza A viruses. The adamantanes are not effective against influenza B viruses; therefore, they are not viable options for the management of contemporary influenza.

Table 4. Influenza-Specific Pharmacotherapy

Agent	Drug Class; Influenza Activity	Bioavailability	Half-life (hr)	Treatment Dosage	Adverse Effects	Comments
Oseltamivir phosphate	Neuraminidase inhibitor; A and B	Orally or OG/NG tube: > 75%	6–10	75 mg twice a day for 5 days[a]; up to 150 mg twice a day has been used in patients with severe influenza but is not associated with improved outcomes and thus is not currently recommended by the CDC	Nausea, vomiting, delirium	Dosage adjustment for renal impairment may be necessary; patients requiring continuous renal replacement therapy should receive normal dosing
Peramivir	Neuraminidase inhibitor; A and B; limited clinical trial experience for Influenza B strains	IV: 100%	20	600 mg once for 15 minutes	Diarrhea, hypersensitivity reactions, delirium	Dosage adjustment recommended in patients with creatinine clearance below 50 mL/min; should be administered after dialysis in patients receiving hemodialysis

Table 4. Influenza-Specific Pharmacotherapy *(continued)*

Agent	Influenza Activity	Bioavailability	Half-life (hr)	Treatment Dosage	Adverse Effects	Comments
Zanamivir	Neuraminidase inhibitor; A and B	Inhaled: Up to 17%	2.5–5	10 mg twice a day for 5 days[a]	Allergic reactions, diarrhea, nausea, headache, dizziness	Not recommended in patients with chronic lung disease or severe influenza; not available for delivery through mechanical ventilator circuit because of bronchospasm
Baloxavir marboxil	Polymerase acidic endonuclease inhibitor; A and B	Tablet, oral: Prodrug converted almost completely to active baloxavir; bioavailability not formally established	79% (53%–96%); primary hepatic metabolism (80% of dose)	Weight 40–79.9 kg: 40 mg orally once; weight ≥ 80 kg: 80 mg orally once	Generally minimal (< 5% of patients): Diarrhea, bronchitis, nausea, sinusitis, headache	93% protein binding; limited data for hospitalized patients with severe influenza
Amantadine	Adamantane; A only	70%–100%	15–17	100 mg twice a day	Nausea, dizziness, insomnia, lower seizure threshold, anticholinergic effects	High resistance to current influenza A strains
Rimantadine	Adamantane; A only	> 90%	24–35	100 mg twice a day	Dizziness, nausea, vomiting; anticholinergic effects	High resistance to current influenza A strains; limited market availability

[a] Longer durations of up to 14 days may be needed for severely ill patients.

IV = intravenous(ly); NG = nasogastric; OG = orogastric.

2. Response to antiviral therapy should be assessed throughout treatment using clinical signs and symptoms of infection. Development of oseltamivir resistance during therapy has been reported, but this is rare. If suggested through local surveillance, therapy should be switched to zanamivir by the appropriate administration route. Improvement in infectious and noninfectious complications may be delayed, despite resolution of primary influenza infection. ARDS, in particular, may persist for days beyond primary influenza.

Patient Cases

19. T.Y., a 32-year-old woman who has had flulike symptoms for the past 72 hours, presents to the ED from home with severe fatigue, shortness of breath, and rigors. T.Y. has a heart rate of 120 beats/minute, mean arterial pressure 70 mm Hg, respiratory rate 24 breaths/minute, temperature 102.7°F (39.3°C), and arterial oxygen saturation (SaO_2) of 85% on room air. Because it is in the middle of influenza season (high prevalence of influenza A and B), a nasal swab is done and sent for rapid diagnostic testing for suspected influenza infection. Shortly thereafter, T.Y. is intubated for severe respiratory failure and admitted to the MICU. In addition to antibiotic therapy for CAP, which would best be considered next?
    A. None; the patient is outside the time window to effectively treat influenza.
    B. Await rapid diagnostic test results before initiating influenza-specific therapy.
    C. Give amantadine.
    D. Give oseltamivir.

20. G.L. is a 25-year-old woman admitted to the medical ICU in late February this year with severe, acute hypoxemic respiratory failure requiring mechanical ventilation. G.L. is hypotensive, requiring norepinephrine after fluid resuscitation, and has acute kidney injury. She is awaiting a renal consult for continuous renal replacement therapy. A rapid diagnostic test of a nasal washing suggests influenza B, consistent with this year's local influenza epidemiology. A nasogastric feeding tube is placed when she is admitted to the ICU. Which would be most appropriate to treat G.L.'s severe influenza?
    A. Enteral amantadine.
    B. Enteral oseltamivir.
    C. Inhaled zanamivir.
    D. Intravenous peramivir.

IX. SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

A. Epidemiology
   1. In late December 2019, a novel coronavirus strain causing pneumonia in a human was first identified in Wuhan, China. This virus, first labeled 2019-nCoV, is now called novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
   2. As of March 10, 2023, there have been more than 676 million cases of SARS-CoV-2 worldwide, with over 6.8 million associated deaths. More than 103 million cases and over 1 million deaths have been attributed to SARS-CoV-2 in the United States (https://coronavirus.jhu.edu/map.html).
   3. Illness related to SARS-CoV-2 is called coronavirus disease 2019 (COVID-19). COVID-19 was categorized as a worldwide pandemic on March 11, 2020.
   4. COVID-19 is characterized by a broad spectrum of illnesses, from mild upper respiratory symptoms to life-threatening respiratory failure, sepsis, and/or multiorgan failure.
   5. Before vaccination and other SARS-CoV-2-directed therapeutics, about 80% of patients with COVID-19 present with mild illness, and 15%–20% present with more severe illness requiring hospitalization. Between 2% and 10% of patients with COVID-19 require ICU admission, accounting for 30%–40% of patients hospitalized with COVID-19.

6. Risk factors for COVID-19–related hospitalization span several comorbidities, including hypertension, diabetes, cardiovascular disease, COPD, obesity, and chronic kidney disease. Patients with comorbidities are at increased risk of hospitalization, ICU admission, and mortality.
    a. The most common complication of COVID-19 in ICU patients is hypoxemic respiratory failure from viral pneumonia, usually bilateral. Cytokine release syndrome or "cytokine storm" with multiorgan failure may be the primary presentation in some patients.
    b. Between 25% and 90% of patients admitted to the ICU require MV.
    c. Additional acute complications: Septic shock, liver dysfunction, bleeding and coagulation dysfunction, cytokine release syndrome, lymphopenia, and acute cerebrovascular disease
    d. Late complications: Myocarditis, cardiomyopathy, and ventricular arrhythmias
7. In-hospital crude mortality for COVID-19 is generally 15%–60%. Rates have declined in areas with higher levels of immunity.
    a. Mortality approaches 40% in ICU patients with COVID-19.
    b. Age-related in-hospital mortality ranges from less than 5% for individuals younger than 40 to greater than 60% for those older than 80.

B. Etiology
1. SARS-CoV-2 is a coronavirus; coronaviruses are relatively large, enveloped, single-stranded RNA viruses. Clinically, coronaviruses are usually associated with the common cold and mild to moderate gastrointestinal illness. Common seasonal strains include coronaviruses 229E, HKU1, NL63, and OC43.
2. SARS-CoV-2, SARS-CoV (SARS), and Middle East respiratory syndrome (MERS) are the most recent coronaviruses to cause severe respiratory infection.
3. SARS-CoV-2 predominantly targets nasal and bronchial epithelial cells and lower respiratory tract epithelial pneumocytes.
4. SARS-CoV-2 pathogenicity is mediated through binding of the viral structural spike protein (S protein) to membrane angiotensin-converting enzyme 2 (ACE2) receptors, predominant in alveolar type II cells. Subsequently, serine protease type 2 transmembrane serine protease (TMPRSS2) cleaves the ACE2 receptor–S protein complex, leading to activation of the viral S protein and enhanced cellular uptake. Once intracellular, SARS-CoV-2 RNA is incorporated into the host nucleus, and viral replication ensues. Activation of the ACE2 receptor may also implicate the contact pathway and complement system, perhaps through an ACE2-mediated increase in bradykinin, in the pathophysiology of COVID-19. This has been hypothesized to be the primary mechanism of cytokine release syndrome in patients with COVID-19.
5. Mutations in SARS-CoV-2 continue to be reported.
    a. One of the first reported variants was D614G, which has a modified S protein that may increase cellular viral uptake. Many areas worldwide are concurrently experiencing multiple SARS-CoV-2 variants.
    b. To date, the Delta variant (B.1.617.2) has demonstrated increased transmissibility (about 2-fold) and pathogenicity compared with the wild-type SARS-CoV-2 strain.

C. Prevention
1. SARS-CoV-2 is primarily transmitted from human to human through respiratory secretions, most likely through droplets. Transmission is also possible through direct surface contact, though this is less likely.
2. Physical distancing, handwashing, and airborne pathogen precautions (i.e., mask wearing) together with contact precautions in medical environments are recommended to decrease transmission.
3. Clinicians caring for patients undergoing aerosol-generating procedures (e.g., endotracheal intubation; bronchoscopy) should don respirator masks together with eye protection and full-body gowning. Negative-pressure patient rooms are preferred during aerosol-generating procedures.

4. The incubation period for SARS-CoV-2 is estimated to be up to 14 days from exposure. Information on onset and duration of viral shedding and infectious potential is still emerging and suggests variable time intervals of 2–18 days from symptom onset. Individuals with symptoms likely have a higher potential for transmitting the virus.
5. Several vaccines against SARS-CoV-2 are available and should be considered per CDC recommended schedules.

D. Diagnosis
1. Primary COVID-19 symptoms in hospitalized patients include fever (80%), dry cough (75%), shortness of breath (70%), fatigue (40%), myalgias (35%), and gastrointestinal symptoms (30%). The most common reason for hospitalization is shortness of breath or hypoxemia.
2. Laboratory abnormalities in hospitalized patients with COVID-19 include:
    a. Lymphopenia (related to T-cell lysis from direct infection by SARS-CoV-2)
    b. Elevated inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate, ferritin, interleukin [IL]-6, tumor necrosis factor alpha). May resemble cytokine release syndrome
    c. Coagulation abnormalities (e.g., prolonged prothrombin time, thrombocytopenia, elevated D-dimer, hypofibrinogenemia)
3. Radiographic abnormalities can vary, but patients with severe disease commonly present with bilateral, lower lobe–predominant infiltrates on chest radiography. Chest CT can reveal bilateral, ground-glass opacities with or without consolidation, usually depending on the time course of presentation.
4. The CDC recommends that nasopharynx samples be used to detect SARS-CoV-2 in patients presenting with COVID-19 symptoms. Lower respiratory tract samples (e.g., endotracheal aspirate, BAL) have a higher diagnostic yield, but concerns with aerosolization and lack of tolerability in those with severe hypoxemia may limit their usefulness.
5. COVID-19 diagnosis is confirmed using RT-PCR.

E. Management and Treatment
1. Management priorities for critically ill patients with COVID-19 include supportive care of hypoxemic respiratory failure and septic shock; immunomodulation of the inflammatory coagulation response, including consideration for anticoagulation; and primary antiviral therapy.
2. New information is emerging on effective management strategies and therapies. Useful resources include the IDSA Guidelines on the Treatment and Management of Patients with COVID-19 (www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) and the Surviving Sepsis Campaign (*Crit Care Med* 2021;49(3):e219-e234). In August 2024, the NIH took down their final guidelines and now defer recommendations to physician specialty groups.
    a. Hypoxemic respiratory failure
        i. Supplemental oxygen to maintain SaO_2 above 92%–96%; high-flow nasal cannula preferred to noninvasive positive pressure ventilation
        ii. For patients who require MV: ARDSNet lung-protective strategy
            (a) Low tidal volumes
            (b) Appropriate plateau pressures
            (c) Higher PEEP (positive end-expiratory pressure)
            (d) Intermittent or continuous (in those for whom intermittent dosing fails) neuromuscular blockade
            (e) Proning
        iii. Extracorporeal membrane oxygenation (ECMO): Venovenous ECMO in patients with refractory hypoxemia despite optimizing ventilation, rescue therapies, and proning
    b. Septic shock
        i. Goal blood pressure: MAP of 60–65 mmHg

- ii. Fluid resuscitation: Conservative management strategy using balanced crystalloid solutions
- iii. Vasopressors: Norepinephrine as first line; vasopressin or epinephrine as second line
- iv. Inotropes: Dobutamine if cardiac dysfunction or persistent hypoperfusion despite fluid resuscitation and norepinephrine
- v. Corticosteroids: See Immunomodulation section in the text that follows.
- vi. Empiric antibiotic therapy should be reserved for patients with confirmed of high suspicion of concomitant bacterial infection.

c. Anticoagulation without contraindication or other compelling indication for therapeutic anticoagulation
- i. Hospitalized patients not requiring oxygen should receive prophylactic heparin
- ii. In non-ICU and non-pregnant hospitalized patients requiring conventional oxygen therapy AND with a d-Dimer above the upper limit of normal should receive therapeutic heparin for 14 days or until they are transferred to the ICU or discharged from the hospital, whichever comes first. Pregnant patients should receive prophylactic heparin as appropriate.
- iii. Hospitalized patients requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO should receive prophylactic heparin.

d. Immunomodulation
- i. Corticosteroids
  - (a) Dexamethasone (or equivalent-dose prednisone, methylprednisolone, or hydrocortisone) 6 mg per day orally or intravenously for up to 10 days or until hospital discharge is recommended for COVID-19 treatment in hospitalized patients requiring increased amounts of supplemental oxygen or MV or ECMO.
    - (1) The largest corticosteroid study to date is the RECOVERY trial, a randomized, open-label trial comparing dexamethasone 6 mg orally or intravenously once daily for up to 10 days with usual care alone in 6425 patients (dexamethasone 2104; usual care 4321) hospitalized with COVID-19. At baseline, 3883 patients required supplemental oxygen, and 1007 required MV.
      - (A) Dexamethasone decreased 28-day mortality (primary outcome) (dexamethasone 22.9% vs. usual care 25.7%; age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $p<0.001$).
      - (B) Results were similar among patients who required MV (29.3% vs. 41.4%; rate ratio 0.64; 95% CI, 0.51–0.81) and those receiving supplemental oxygen (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94). There was no difference among patients not requiring respiratory support.
  - (b) The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group conducted a meta-analysis of seven controlled trials encompassing 1703 critically ill patients (requiring supplemental oxygen or MV) with COVID-19, including 1007 patients (15.7% of end enrollment) enrolled early in RECOVERY, showed that corticosteroids were associated with lower 28-day all-cause mortality compared with placebo or usual care (OR 0.66 [95% CI, 0.53–0.82]; $p<0.001$).
  - (c) The prospective, randomized, controlled COVID STEROID 2 trial evaluated dexamethasone 6 mg or 12 mg daily for up to 10 days in 982 hospitalized patients.
    - (1) Median number of days alive without life support at 28 days was 20.5 days (interquartile range [IQR] 4.0–28.0) vs. 22.0 days (IQR 6.0–28.0) (adjusted mean difference 1.3 days (95% CI, 0–2.6; $p=0.07$).
    - (2) No difference was found in 28-day or 90-day mortality.
- ii. Other immunomodulators
  - (a) Toclizumab: Anti-IL-6 receptor monoclonal antibody (alternative class agent: sarilumab)

(1) The COVACTA trial (N Engl J Med 2021;384:1503-16) was a randomized, placebo-controlled trial in 438 hospitalized adults with severe COVID-19 pneumonia.
  (A) Patients were randomized 2:1 to either a single intravenous infusion of tocilizumab (8 mg/kg actual body weight) or placebo; 25% of patients received a second dose of tocilizumab.
  (B) At enrollment, 37% of patients required MV and 22.4% received concomitant corticosteroids.
  (C) No between-group differences were observed in clinical progression or 28-day mortality (tocilizumab, 19.7% vs. placebo, 19.4%; weighted difference 0.3%; 95% CI, –7.6 to 8.2).

(2) The REMAP-CAP trial (N Engl J Med 2021;384:1491-502) randomized 803 patients within 24 hours of ICU admission (median 1.2 days from hospitalization) to open-label tocilizumab 8 mg/kg actual body weight (max of 800 mg) (353 patients), sarilumab 400 mg (48 patients), or standard of care (402 patients).
  (A) Most patients (552 [68.7%]) were free of MV and/or ECMO at enrollment; 76% of patients received concomitant corticosteroids.
  (B) Tocilizumab was associated with reduced in-hospital mortality (28% vs. 36%; OR 1.64; 95% CI, 1.25–2.14) and higher median days free of respiratory and cardio-vascular organ failure (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14).
  (C) Tocilizumab was also associated with decreased progression to MV, ECMO, or death (OR 0.59; 95% CI, 0.41–0.86).

(3) The RECOVERY trial (Lancet 2021;397:1637-45) was a randomized, controlled, open-label study in 4116 hospitalized patients with COVID-19 demonstrating acute hypoxia and evidence of systemic inflammation (i.e., C-reactive protein ≥75 mg/L).
  (A) Patients were randomized 1:1 ratio to usual care vs. usual care plus tocilizumab 400 mg–800 mg intravenously once; 29% of tocilizumab patients received a second dose at provider discretion.
  (B) At enrollment, 82% of patients received concomitant corticosteroids and 13.8% required MV.
  (C) Tocilizumab was associated with a decreased 28-day mortality overall (tocilizumab, 31% vs. usual care, 35%; rate ratio 0.85; 95% CI 0.76–0.94) and across prespeci-fied subgroups based on illness severity.
  (D) Patients not requiring MV at enrollment who received tocilizumab were less likely to progress to MV or death (35% vs 42%; risk ratio 0.84; 95% CI 0.77–0.92).

(4) Tocilizumab is authorized for use under an FDA Emergency Use Authorization (EUA) for treatment of COVID-19 in hospitalized patients from 2 to less than 18 years of age who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO. On December 21, 2022, the FDA approved tocilizumba for the treatment of COVID-19 in hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

(5) Possible adverse effects include serious infections, fungal pneumonia, gastrointestinal perforation, hepatotoxicity, and cytopenias.

(b) Baricitinib: Janus kinase inhibitor (alternative class agent: tofacitinib)
  (1) The ACTT-2 study (N Engl J Med 2021;384:795-807) was a double-blind, randomized, placebo-controlled trial evaluating baricitinib 4 mg/day orally or via nasogastric tube plus remdesivir (200 mg on day one, then 100 mg daily for 5-10 days) versus placebo in 1033 hospitalized patients with COVID-19.

(A) At enrollment, 32% of patients had severe disease, with 10.7% of patients requiring MV or ECMO. Patients receiving corticosteroids for COVID-19 were excluded.

(B) Overall, patients receiving baricitinib plus remdesivir had a shorter time to recovery (7 days; 95% CI 6–8 vs. 8 days; 95% CI 7–9; rate ratio 1.16; 95% CI, 1.01–1.32), which was most pronounced in patients receiving high-flow oxygen or noninvasive ventilation at enrollment (10 days vs. 18 days; rate ratio 1.51; 95% CI, 1.10–2.08).

(C) No difference was noted in 28-day mortality (5.1% vs. 7.8%; hazard ratio 0.65; 95% CI 0.39–1.09).

(2) The COV-BARRIER trial (Lancet Respir Med 2021; www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00331-3/fulltext) was a multinational, placebo-controlled, randomized trial in 1525 hospitalized patients with COVID-19 pneumonia and elevated inflammatory markers. Patients receiving MV were excluded.

(A) Patients were randomized 1:1 to receive baricitinib 4 mg/day (renally-adjusted as necessary) orally or placebo in addition to usual care; 92% of patients received concomitant dexamethasone.

(B) No between-group difference were noted in disease progression.

(C) Patients receiving baricitinib overall had lower 28-day all-cause mortality (8% vs. 13%; hazard ratio 0.57; 95% CI 0.41–0.78).

(D) The treatment effect for mortality was most notable among the subgroup of 370 pa-tients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% vs. 29.4%; hazard ratio 0.52; 95% CI, 0.33–0.80).

(3) The COV-BARRIER Addendum was an exploratory randomized, placebo-controlled trial evaluating baricitinib in 101 patients with confirmed COVID-19 and 1 or more elevated inflammatory markers (CRP, D-dimer, LDH, or ferritin) and MV or ECMO (Lancet Respir Med 2022;10:327-36).

(A) Patients were randomized 1:1 to receive baricitinib 4 mg/day (renally-adjusted as necessary) orally or placebo in addition to usual care; 86% of patients received concomitant dexamethasone.

(B) 28-day mortality: baricitinib 39% versus placebo 58% (hazard ratio 0.54; 95% CI, 0.31–0.96; p=0.030). Baricitinib relative reduction in mortality similar as seen in less severely ill population from COV-BARRIER parent trial.

(C) Number of ventilator-free days and duration of hospitalization: no significant difference between arms

(4) Baricitinib use is supported by an FDA EUA for treatment of COVID-19 in hospitalized patients from 2 to less than 18 years of age requiring supplemental oxygen, non-invasive or invasive MV, or ECMO. Baricitinib was approved on May 10, 2022, for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO.

(5) Baricitinib can be administered orally or via oral dispersion or gastrostomy or nasogastric tube.

(6) Possible adverse effects include elevations of transaminases, fungal pneumonia, thrombosis, and cytopenias.

(c) Although preclinical models and early clinical reports have been enthusiastic, data are insufficient to support routine use of other immunomodulators in patients with COVID-19. Ongoing clinical trials are anticipated. Additional drug classes/agents reported include:

(1) IL-1 inhibitors (e.g., anakinra)

(2) Interferon alfa or beta

- (3) Anti–IL-6 monoclonal antibody siltuximab
- (4) Bruton tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib)

e. Antiviral therapy

- i. Remdesivir
  - (a) Nucleotide prodrug of adenosine analog that binds to viral RNA polymerase, terminating RNA transcription and inhibiting viral replication. Initially developed to treat MERS
  - (b) FDA-approved as Veklury for adult and pediatric (12 years or older and weighing at least 40 kg) patients hospitalized with COVID-19
    - (1) Dosage: 200 mg intravenously once, then 100 mg intravenously daily for 5 days; 10 days' duration can be considered in patients with no clinical improvement after 5 days
    - (2) Precautions include patients with baseline liver dysfunction, particularly those with elevated alanine aminotransferase.
  - (c) Recommended in hospitalized patients who require supplemental oxygen with or without corticosteroids or those patients at high risk for decompensation or immunocompromised.
    - (1) Should only be used in combination with corticosteroids in patients requiring high-flow oxygen; not recommended in patients requiring MV or ECMO because benefit is uncertain in subgroups of more severely ill patients.
    - (2) If supplies are limited, prioritize use for patients not requiring high-flow oxygen; not recommended in patients requiring MV or ECMO.
  - (d) To date, the largest published, placebo-controlled trial is the Adaptive COVID-19 Treatment Trial (ACTT-1), which compared remdesivir with placebo in 1063 patients hospitalized with COVID-19 and receiving standard of care.
    - (1) Primary outcome was the time to recovery within 28 days, defined as the first day of clinical improvement to categories 1–3 on an ordinal scale ranging from 1, not hospitalized, return to usual care; to 3, hospitalized, not requiring supplemental oxygen; to 8, death. All patients had scores of 4–7 at enrollment. At baseline, 197 patients (18.5%) required high-flow supplemental oxygen (score of 6), and 292 (25.6%) required MV or ECMO (score of 7).
    - (2) Patients receiving remdesivir had a shorter time to recovery (median 11 days vs. 15 days; rate ratio 1.32; 95% CI, 1.12–1.55; $p<0.001$). Among patients with baseline scores of 6 and 7, rate ratios for time to recovery were 1.20 (95% CI, 0.79–1.81) and 0.95 (95% CI, 0.64–1.42), respectively.
    - (3) Rate ratio for 14-day mortality among all patients was 0.70 (95% CI, 0.47–1.04), with the greatest treatment effect in the largest patient subgroup (n=421) with a baseline score of 5 (rate ratio 0.22 [95% CI, 0.08–0.58]). Corresponding rate ratios among patients with baseline scores of 6 and 7 were 1.12 (95% CI, 0.53–2.38) and 1.06 (95% CI, 0.59–1.92), respectively.
    - (4) Adverse effects were generally similar between groups.
  - (e) The prospective, randomized, open-label WHO SOLIDARITY Trial compared remdesivir to standard of care in 8275 hospitalized patients with COVID-19 requiring supplemental or high-flow oxygen (71%) or mechanical ventilation (9%) (Lancet 2022;399:1941-53).
    - (1) Patients were randomized 1:1 to remdesivir standard dosing for 10 days or standard of care; 68% of patients received corticosteroids.
    - (2) In-hospital mortality: remdesivir 14.5% versus standard of care 15.6 (rate ratio 0.91; 95% CI, 0.82–1.02; $p=0.12$)
    - (3) Patients receiving oxygen: 14.6% versus 16.3% (rate ratio 0.87; 95% CI, 0.76–0.99; $p=0.03$)
    - (4) Progression to mechanical ventilation: 14.1% versus 15.7% (rate ratio 0.88; 95% CI, 0.77–1.00; $p=0.04$)

ii. Hydroxychloroquine or chloroquine
  (a) Antimalarial agents that, in vitro, increase the endosomal pH, inhibiting fusion of SARS-CoV-2 to the host cell membranes
  (b) Not recommended as definitive or prophylactic therapy because larger controlled trials have failed to show a difference in clinical recovery or mortality in hospitalized patients with COVID-19
  (c) Combination with azithromycin reserved for clinical trial

iii. Miscellaneous agents
  (a) Ivermectin: Not recommended; evidence does not support use for patients with COVID-19
  (b) Lopinavir/ritonavir and other HIV protease inhibitors: Not recommended outside clinical trial
  (c) Nirmatrelvir-ritonavir, although FDA approved for the treatment for mild-moderate COVID-19, may reduce 28-day risk of all-cause mortality in critically ill patients with COVID-19 and in patients at high risk of critical disease progression (*J Intensive Care Med*. 2024;39(8):742-750).

Table 5. National Institutes of Health Guideline Recommendations for Pharmacologic Management of Patients Hospitalized with Coronavirus Disease 2019

Disease Severity	Remdesivir	Dexamethasone[a]	Baricitinib	Tocilizumab[b]	Anticoagulation
No supplemental oxygen requirement	Consider patients at high risk for worsening	Against use	N/A	N/A	For patients without an indication for therapeutic anticoagulation: Prophylactic dose of heparin, unless contraindicated (AI)
Supplemental oxygen required	Recommended in patients with *minimal oxygen requirement*	Recommended in combination with remdesivir in most patients requiring oxygen; may use alone if remdesivir is unavailable	Patients who have rapidly increasing oxygen needs and systemic inflammation, promptly add either agent (rating recommendation/ evidence level: baricitinib BIIa; tocilizumab BIIa) to dexamethasone ± remdesivir in most patients		For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: Therapeutic dose of heparin (CIIa) For other patients: Prophylactic dose of heparin, unless contraindicated (AI)

Table 5. National Institutes of Health Guideline Recommendations for Pharmacologic Management of Patients Hospitalized with Coronavirus Disease 2019 *(continued)*

Disease Severity	Remdesivir	Dexamethasone[a]	Baricitinib	Tocilizumab[b]	Anticoagulation
High-flow oxygen device or noninvasive ventilation requirement	Recommended in combination with dexamethasone	Recommended as preferred therapy with or without remdesivir	Promptly add either agent (rating recommendation/ evidence level: baricitinib AI; tocilizumab BIIa) to dexamethasone ± remdesivir in most patients		For patients without an indication for therapeutic anticoagulation: Prophylactic dose of heparin, unless contraindicated (AI) For patients on therapeutic dose of heparin in non-ICU setting and transferred to ICU, switch to prophylactic dose of heparin, unless another indication for therapeutic anticoagulation (BIII)
Mechanical ventilation or extracorporeal membrane oxygenation requirement	N/A	Recommmeded to be administered to all patients (AI).	Promptly add either agent (Rating recommendation/ Evidence level: baricitinib BIIa; tocilizumab BIIa) to dexamethasone in most patients		

[a] Alternative corticosteroids at equivalent glucocorticoid dose may be considered.

[b] Although approximately 33% of REMAP-CAP and RECOVERY patients received a second dose of tocilizumab at the treating physician's discretion, evidence to support repeat dosing is insufficient.

N/A = No recommendation provided.

Information from: National Institutes of Health (NIH); COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Previously available at www.covid19treatmentguidelines.nih.gov/about-the-guidelines/table-of-contents/. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637-45; REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384:1491-502. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med 2022;10:327-36; WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. Lancet 2022;399:1941-53.

Patient Case

21. S.B. is a 48-year-old woman with severe obesity and heart disease intubated emergently at an outside hospital for refractory hypoxemic respiratory failure despite maximal MV support. S.B. is being evaluated for venovenous ECMO. She is quickly transferred to the MICU for evaluation. S.B. is initiated on dexamethasone 6 mg intravenously once daily, and her analgesia-sedative regimen is modified to maintain deep sedation in anticipation of starting continuous neuromuscular blockade. S.B. is receiving norepinephrine at 10 mcg/minute, which continues to be tapered to maintain a mean arterial pressure greater than 65 mm Hg. S.B. is being considered for remdesivir, which is in ample supply at your institution. Which best describes the current guideline recommendations for remdesivir in patients with COVID-19 requiring MV?

    A. Shown to decrease in-hospital mortality.
    B. Not recommended because of safety concerns.
    C. Recommended to shorten time to clinical recovery.
    D. Uncertain benefit on clinical recovery and mortality.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: A**

The patient has suspicion for MDR VAP, as evidenced by the presence of clinical signs of infection, the patient's increased sputum production, and the patient's having been in the ICU for 5 days or longer. Empiric antibiotic therapy should be initiated after obtaining a respiratory culture and be based on patient-specific risk factors for MDROs, together with local pathogen prevalence and antibiotic susceptibility, to increase the likelihood of providing timely appropriate antibiotic therapy (Answer A is correct). Gram stain results can be used to help guide empiric therapy as per GRACE-VAP, but antibiotics should not be delayed 1–2 days awaiting Gram stain, preliminary or final respiratory culture results, as well as blood or urine cultures, may cause an unacceptable delay in appropriate antibiotic therapy (Answers B–D are incorrect).

2. **Answer: B**

Although this patient is suspected of having early-onset VAP for the current admission, a history of recent intravenous antibiotic therapy is a risk factor for MDROs. Empiric antibiotic therapy for VAP in patients with MDRO risk factors should include agents active against *P. aeruginosa* and MRSA. Empiric combination therapy against *P. aeruginosa* is recommended to increase the likelihood of appropriate antibiotic therapy (Answer B is correct; Answers A and C are incorrect) with a β-lactam antibiotic as one of the preferred agents (Answer D is incorrect). Atypical bacteria coverage is not necessary because their prevalence is low, although consideration should be given if there is a poor response to initial therapy.

3. **Answer: B**

Based on the PneumA trial and related meta-analyses, the most recent IDSA VAP guidelines recommend definitive antibiotic therapy duration of 7 full treatment days for all patients. This is further emphasized in this patient, who has VAP caused by *Klebsiella* spp., which are lactose-fermenting gram-negative bacilli, and who received appropriate empiric antibiotic therapy and had an appropriate clinical response during therapy (Answer B is correct; Answers A, C, and D are incorrect).

4. **Answer: D**

In the absence of other suspected sources (i.e., no change in chest radiograph), CLABSI should be suspected as the cause of new-onset fever and leukocytosis, given the emergency placement and related duration of the CVC (Answer B is incorrect). Although catheter removal should strongly be considered, cultures should be obtained before catheter removal for documentation if the patient has a bloodstream infection (Answer C is incorrect). Initiation of antibiotic therapy should be considered, if appropriate, but only after cultures of the suspected source are obtained (Answer D is correct; Answer A is incorrect).

5. **Answer: D**

This patient, who is thought to have a CLABSI, has risk factors for MDROs, given that the patient was hospitalized for 5 or more days. Empiric antibiotic therapy choices should include agents active against MRSE and MRSA as well as *P. aeruginosa* (Answer D is correct; Answer A is incorrect). Linezolid is active against MRSA; however, it should be considered only for definitive therapy because its empiric use in patients with a CLABSI is associated with worse outcomes (Answer C is incorrect). Fluconazole may be considered in addition to antibiotic therapy, but monotherapy is not recommended empirically (Answer B is incorrect).

6. **Answer: B**

The guideline recommendation for definitive antibiotic therapy duration is 7–14 days from the first negative blood culture in patients with uncomplicated gram-negative CLABSI. Longer durations of therapy should be considered in patients with persistent bacteremia or if the patient has a poor clinical response. (Answer B is correct; Answers A and C are incorrect). Patients with complicated bacteremia (e.g., endocarditis, septic thrombus, chronic intravascular hardware) should receive 4-6 weeks of therapy (Answer D is incorrect).

7. **Answer: C**

The presence of new fever and an elevated WBC in conjunction with an indwelling urinary catheter and pyuria on urinalysis is highly suggestive of a CAUTI rather than worsening pneumonia (Answer B is incorrect). Similar to other ICU-related infections, empiric antibiotic therapy should be considered if there is strong clinical suspicion for infection (Answer C is correct). Waiting for final culture results before initiating antimicrobial therapy in patients thought to have a CAUTI may delay appropriate treatment (Answer A is incorrect). Although it is recommended to discontinue the urinary catheter and replace as necessary, a confirmatory urinalysis is not needed if the catheter has been indwelling for less than 2 weeks (Answer D is incorrect).

8. **Answer: B**

The patient had an appropriate clinical response to therapy in less than 72 hours and should be limited to 7 days of effective therapy (Answer B is correct). Fourteen days of therapy is appropriate if the patient shows clinical signs and symptoms of infection after 72 hours of effective therapy (Answer D is incorrect). There are no recommendations for antibiotic courses of 5 or 10 days in the treatment of CAUTI (Answers A and C are incorrect).

9. **Answer: D**

This patient has complicated intra-abdominal infection from secondary peritonitis caused by colonic perforation. Although it is community acquired, the presence of septic shock suggests severe classification increasing the risk of gram-negative MDROs (Answer C is incorrect). The involvement of the colon also obligates antibiotic therapy active against anaerobes and enterococci (Answer B is incorrect); MRSA is an unlikely pathogen (Answer A is incorrect). According to this, piperacillin/tazobactam is the most appropriate agent listed (Answer D is correct).

10. **Answer: A**

The approach to managing a complicated intra-abdominal infection includes timely source control and initiation of empiric antimicrobial therapy active against likely pathogens. This involves assessment of the anatomic location of the source, risk factors for multidrug-resistant organisms (i.e., community- or health care–associated disposition), and severity of illness. This patient has community-acquired secondary peritonitis from a distal small bowel perforation with concomitant septic shock. Although his disease is community acquired, the presence of septic shock suggests a severe classification, increasing the risk of gram-negative multidrug-resistant organisms and involvement of the distal small bowel obligates empiric coverage for anaerobic pathogens and enterococci, for all of which meropenem plus linezolid should provide appropriate empiric coverage (Answer A is correct). Ertapenem would likely have adequate empiric coverage for enteric, gram-negative pathogens, both aerobic and anaerobic; however, lack or enterococcal coverage makes it less optimal (Answer B is incorrect). Ciprofloxacin lacks sufficient activity against enterococci or anaerobic pathogens, and MRSA coverage with vancomycin is unnecessary (Answer C is incorrect). Cefazolin is too narrow as empiric therapy for a severe community-acquired complicated intra-abdominal infection, and fluconazole should be reserved for definitive therapy for fluconazole-susceptible yeast identified on final culture (Answer D is incorrect).

11. **Answer: B**

Shorter durations of antimicrobials have shown outcomes similar to longer durations (Answers C and D are incorrect). Although 4 or 5 days of therapy has been shown in the general population, data are limited in the critically ill population (Answer A is incorrect). The SIS recommends a limit of 8 days of antimicrobial therapy after source control in critically ill patients (Answer B is correct).

12. **Answer: D**

Acute necrotizing pancreatitis often presents with signs and symptoms consistent with systemic inflammatory response syndrome. However, most cases of severe necrotizing pancreatitis are sterile and do not require antibiotic therapy. The presence of a pancreatic pseudocyst or abscess increases the likelihood of infected necrotizing pancreatitis, which thus warrants empiric antimicrobial therapy. However, this patient has no evidence of these on CT scan; thus, empiric antibiotic therapy is not indicated (Answers A–C are incorrect). Moreover, prophylactic antimicrobial therapy is not recommended in the recent guidelines, despite the presentation of systemic inflammation and pancreatic necrosis (Answer D is correct). A prospective, randomized, noninferiority study most strongly supports these recommendations.

13. **Answer: D**

This patient has acute, severe pancreatitis with CT evidence of pancreatic abscess. Gram stain of fluid obtained from CT-guided drainage suggests the presence of gram-negative bacilli and yeast (Answer A is incorrect). Empiric antimicrobial therapy is indicated for suspected infected pancreatitis. Extended-spectrum carbapenems, which achieve relevant pancreatic fluid concentrations, are effective in the management of infected pancreatitis. Addition of anti-candidal therapy is indicated, given the presence of yeast on the Gram stain (Answer D is correct; Answers B and C are incorrect).

14. **Answer: B**

This patient is thought to have fulminant (IDSA 2017) CDI, given his recent exposure to broad-spectrum antibiotic therapy, signs of infection, CT findings, and the presence of hypotension. Combination therapy with metronidazole and enteral vancomycin is indicated (Answers A and D are incorrect). The presence of ileus requires consideration of adding intracolonic vancomycin because of possible impaired delivery to the colon through enteral routes (Answer B is correct; Answer C is incorrect).

15. **Answer: D**

The patient in this case presents with what is likely an initial-episode, severe CDI, as supported by new-onset diarrhea and clinical signs and symptoms of infection. Of note, the patient is not hypotensive and has a lactate below 2–4 mmol/L, suggesting the absence of shock or other defining features of fulminant CDI; thus, monotherapy with enteral vancomycin is the best available answer (Answer D is correct). Although the 2021 IDSA/SHEA focused guideline update recommends fidaxomicin for non-fulminant, first-episode CDI, oral/enteral vancomycin is an acceptable alternative, especially if fidaxomicin is unavailable. Combination therapy with oral/enteral vancomycin and intravenous metronidazole should be reserved for a complicated CDI (Answer C is incorrect), and intravenous metronidazole is not recommended (Answer B is incorrect). The combination of metronidazole and intracolonic is recommended for patients with a complicated CDI and concern for ileus or inability to deliver oral/enteral vancomycin to the colon (Answer A is incorrect).

16. **Answer: B**

For an initial severe episode of CDI, the guidelines recommend that the patient receive either fidaxomicin or vancomycin for 10 days (Answer B is correct). A duration of 14 days could be considered for patients receiving metronidazole when vancomycin or fidaxomicin is unavailable (Answer C is incorrect). Duration of 5 days or 4 weeks is not supported for the initial treatment of CDI (Answers A and D are incorrect).

17. **Answer: C**

Necrotizing fasciitis is a severe, life-threatening infection that is often polymicrobial. Prompt surgical debridement of necrotic tissue and broad-spectrum antibiotic therapy are the mainstays of initial therapy. Agents active against *S. pyogenes*, MRSA, and aerobic and anaerobic gram-negative bacilli should be initiated empirically, together with adjunctive clindamycin added, which may decrease bacterial toxin production. The empiric regimen of piperacillin/tazobactam, vancomycin, and clindamycin is most appropriate, given the severity of infection despite the absence of traditional multidrug-resistant organism risk factors (Answer C is correct). Penicillin G is not broad enough (Answer B is incorrect), and the combination of ceftaroline and vancomycin does not contain clindamycin (Answer A is incorrect). Combination of clindamycin and linezolid do not include empiric gram-negative coverage. (Answer D is incorrect).

18. **Answer: B**

The intraoperative cultures of this patient's necrotizing infection are of concern for *S. pyogenes*. *S. pyogenes* produces exotoxin, which is associated with tissue necrosis. Although bactericidal antibiotic therapy is necessary for eradicating *S. pyogenes*, adjunctive clindamycin may decrease toxin production, which could limit the extent of tissue necrosis (Answer B is correct). Vancomycin should be reserved for patients with an *S. pyogenes* infection who have a β-lactam allergy because β-lactam resistance is rare (Answer C is incorrect). Moreover, synergistic antibiotic therapy with gentamicin is not needed, given the effectiveness of gram-positive β-lactams against *S. pyogenes* (Answer A is incorrect). The role of IVIG in streptococcal necrotizing fasciitis is controversial. A small randomized, placebo-controlled trial – stratified on the basis of need for surgery and clindamycin treatment – showed no improvement in survival or reduction in the time to no further progression of necrotizing fasciitis or cellulitis in 21 patients with streptococcal toxic shock syndrome. As such, the guidelines do not recommend IVIG until additional studies are available (Answer D is incorrect).

19. **Answer: D**

This patient likely has severe influenza amid a local seasonal outbreak. Local infection patterns suggest a prevalence of influenza A and B strains. Empiric influenza-specific therapy against these strains should be initiated in patients with severe influenza before confirmatory test results are known to avoid a delay in appropriate therapy (Answer B is incorrect). Neuraminidase-based therapy is recommended for modern influenza A and B stains (Answer D is correct; Answer C is incorrect). Even if they are outside 48 hours from symptom onset, patients with severe influenza have benefited from therapy initiated beyond this period (Answer A is incorrect).

20. **Answer: B**

Neuraminidase inhibitors are the mainstay of treatment because resistance to adamantanes has developed in contemporary influenza A strains, and these agents have no antiviral activity against influenza B (Answer A is incorrect). Inhaled zanamivir is not appropriate for administration to mechanically ventilated patients (Answer C is incorrect). Intravenous peramivir also is available; however, data are limited for its use in critically ill patients with severe, complicated influenza infection (Answer D is incorrect). Enteral oseltamivir is the preferred therapy for current influenza B strains in critically ill patients with severe, complicated influenza infection (Answer B is correct). Clinicians should be mindful of the need for renal dosage adjustment, if necessary.

21. **Answer: D**

Remdesivir is recommended for patients requiring supplemental oxygen. On the basis of the results of the ACTT study showing no difference in recovery time or mortality in more severe subgroups, the NIH guidelines do not recommend for or against remdesivir in patients requiring high-flow oxygen, MV, or ECMO (Answer D is correct; Answers A and C are incorrect). If remdesivir is initiated before advancing to MV, it is recommended to continue and complete therapy. Available evidence guidelines do not suggest increased adverse effects with remdesivir between less and more severely ill patients (Answer B is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: D**

The patient described has early onset VAP without apparent updated risk factors for MDROs (Answers A, B, and C, are incorrect). Pathogens associated with early onset hospital-acquired pneumonia and VAP in the absence of other MDR risk factors are usually community-acquired organisms, including *S. pneumoniae*, MSSA, *H. influenzae*, and enteric gram-negative bacilli (Answer D is correct). However, because some epidemiological studies have documented the occurrence of traditionally nosocomial or late-onset pathogens within 5 days from admission, guideline updates recommend that *P. aeruginosa* coverage be considered as empiric therapy for all patients suspected of having VAP. This further emphasizes the importance of understanding local VAP pathogen trends amid MDR risk factors and time from admission to onset. Atypical bacteria are rarely associated with early onset VAP. If MDRO risk factors were present, MRSA and *P. aeruginosa* would also be considered.

2. **Answer: B**

Empiric antibiotic choices for VAP should be based on the likely causative pathogens, the presence of MDRO risk factors, and local antibiotic susceptibility patterns. The 2016 IDSA guidelines recommend *P. aeruginosa* coverage as empiric therapy for all patients suspected of having VAP, with monotherapy antipseudomonal β-lactam sufficient in the absence of MDRO risk factors or if the local antibiogram suggests less than 10% resistance. Therefore, cefepime is preferred to ceftriaxone (Answer B is correct; Answers C and D are incorrect). Atypical bacteria are rarely associated with early-onset VAP (Answer A is incorrect).

3. **Answer: D**

Gram-positive organisms are the most common cause of CLABSI, including MRSE and MRSA. Vancomycin is the best option listed for empiric management (Answer D is correct). Although linezolid has a sufficient spectrum of activity against these organisms, it is not recommended for empiric management of CLABSI because of concerns for worse patient outcomes (Answer B is incorrect). The other options are inactive against MRSE and MRSA and could be considered in addition to vancomycin if there were a high suspicion for additional pathogens (Answers A and C are incorrect).

4. **Answer: D**

Given the high prevalence of the 2009 H1N1 subtype of influenza A, oseltamivir is the empiric drug of choice. In addition, oseltamivir has high-level activity against other contemporary influenza A and B subtypes (Answer D is correct). Zanamivir also has high-level activity against these strains; however, inhaled therapy through the mechanical ventilator is not indicated because of insufficient systemic delivery, and intravenous zanamivir is available through compassionate use and indicated only if oseltamivir cannot be administered (e.g., patient is unable to receive enteral medications, has poor absorption) (Answers B and C are incorrect). Amantadine has insufficient activity against most contemporary influenza A and B strains (Answer A is incorrect).

5. **Answer: B**

Although a health care–associated CAUTI is caused by a more diverse spectrum of pathogens, *E. coli* is still the most common pathogen and is responsible for around 30% of cases (Answer B is correct). The other pathogens listed are also possible and should be considered when choosing empiric antibiotic therapy in patients with a suspected CAUTI (Answers A, C, and D are incorrect).

6. **Answer: D**

This patient has community-acquired complicated intra-abdominal infection involving the middle small intestine. Although enteric gram-negative bacilli (e.g., *E. coli*, *Klebsiella* spp.) are the most common pathogens related to this type of infection, patients with severe disease, as evidenced by concomitant septic shock, are at a higher risk of MDROs, including *P. aeruginosa* and enterococci. Piperacillin/tazobactam has empiric activity against these organisms, whereas the other regimens/agents listed have relevant gaps in the bacterial spectrum relative to these pathogens (Answer D is correct; Answers A–C are incorrect).

7. **Answer: A**

This patient presents with severe acute pancreatitis with radiographic evidence of pancreatic necrosis. Although the patient presents with SIRS, the absence of significant fluid collection or abscess suggests there is no concomitant infection. As such, there is no indication for empiric antibiotic therapy at this time (Answer A is correct; Answer B is incorrect). Most recent evidence and guideline recommendations do not support prophylactic antibiotic therapy for preventing infection of the necrotic tissue (Answer D is incorrect). The mainstay of therapy for this patient is volume resuscitation and consideration of surgical debridement of pancreatic necrosis if persistent SIRS is evident (Answer C is incorrect).

8. **Answer: A**

Metronidazole orally or through a feeding tube is not recommended for management of an initial-episode CDI (Answer B is incorrect). Intravenous metronidazole is indicated for fulminant CDI in combination with vancomycin (Answer C is incorrect) In the absence of fulminant CDI (i.e., shock, megacolon, ileus), the 2021 IDSA focused guideline update recommends fidaxomicin over oral/enteral vancomycin for first-episode CDI to increase the likelihood of complete clinical response (Answer A is correct; Answer D is incorrect). If fidaxomicin is unavailable or cost-prohibitive, oral/enteral vancomycin is an acceptable alternative.

9. **Answer: A**

This patient has a superficial incisional wound infection requiring opening and the local debridement of infected material. Lack of systemic signs of infection and no involvement of the fascia suggest that no antibiotic therapy is necessary at this time (Answer A is correct; Answers B–D are incorrect). If the infection extends to include these features or worsened erythema consistent with cellulitis, empiric antibiotic therapy may be warranted.

10. **Answer: A**

The RECOVERY trial showed that dexamethasone decreases 28-day mortality compared with usual care in hospitalized patients with COVID-19 requiring supplemental oxygen or MV. A meta-analysis of available trials also supports corticosteroid use (Answer A is correct). Hydroxychloroquine has limited to no benefit in patients hospitalized with COVID-19 (Answer B is incorrect). Evidence from the ACTT study showed that remdesivir may shorten the duration to clinical recovery, but it has no difference on mortality compared with placebo. Non-controlled, aggregated data have suggested an association with lower mortality, but this has not been confirmed in controlled trials; therefore, remdesivir should be considered in addition to dexamethasone rather than monotherapy in patients with increasing oxygen requirement (Answer C is incorrect). Tocilizumab, an anti–IL-6 monoclonal antibody, can be considered in addition to dexamethasone with or without remdesivir in patients recently hospitalized and demonstrating rapid decline in oxygenation and systemic inflammation. (Answer D is incorrect).

INFECTIOUS DISEASES II

GABRIELLE GIBSON, PHARM.D., FCCM, BCCCP, BCPS

BARNES-JEWISH HOSPITAL
ST. LOUIS, MISSOURI

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BARNES-JEWISH HOSPITAL
ST. LOUIS, MISSOURI

Learning Objectives

1. Compose a plan to incorporate quality metrics (e.g., prevention of catheter-associated urinary tract infections and catheter-related bloodstream infections) into pre- and postsurgical care.
2. Identify key members of, common strategies, and tools (including biomarkers and rapid diagnostic tests) used by an antimicrobial stewardship team.
3. Provide empiric antibiotic therapy recommendations for critically ill patients with community-acquired or health care–associated meningitis.
4. Evaluate therapeutic options for the treatment of multidrug-resistant pathogens in the intensive care unit (ICU).
5. Devise an optimal treatment plan for critically ill immunocompromised patients with infectious diseases.

Abbreviations in This Chapter

ACS NSQIP	American College of Surgeons National Surgical Quality Improvement Program
ASP	Antibiotic stewardship program
AST	Antimicrobial susceptibility testing
CAUTI	Catheter-associated urinary tract infection
CDC	Centers for Disease Control and Prevention
CLABSI	Central line–associated bloodstream infection
CLSI	Clinical & Laboratory Standards Institute
CMS	Centers for Medicare & Medicaid Services
CNS	Central nervous system
CoNS	Coagulase-negative *Staphylococci*
CRE	Carbapenem-resistant Enterobacterales
CSF	Cerebrospinal fluid
CVC	Central venous catheter
ESBL	Extended-spectrum β-lactamase
HAART	Highly active antiretroviral therapy
IDSA	Infectious Diseases Society of America
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
LOS	Length of stay
MALDI-TOF	Matrix-assisted laser desorption-ionization/time of flight
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NHSN	National Healthcare Safety Network
OI	Opportunistic infection
PCR	Polymerase chain reaction
PCT	Procalcitonin
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNA FISH	Peptide nucleic acid fluorescence in situ hybridization
SCIP	Surgical Care Improvement Project
SOT	Solid organ transplantation
SSI	Surgical site infection
TJC	The Joint Commission
UTI	Urinary tract infection
WHO	World Health Organization

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 56-year-old man (weight 140 kg) is scheduled to have elective coronary artery bypass surgery with aortic valve bioprosthetic replacement. The patient has a medical history of diabetes and hypertension. He has no drug allergies and has a calculated CrCl of 90 mL/minute/1.73 m^2. It is anticipated that the patient will be admitted to the cardiovascular surgery ICU after the surgery with two chest tubes placed for drainage. Which is the most appropriate antimicrobial prophylactic regimen for the patient?
   A. Cefazolin 2 g once within 2 hours before incision and administered every 8 hours until chest tubes are removed.
   B. Vancomycin 2 g once within 2 hours before incision and administered every 12 hours until 48 hours after surgery.
   C. Cefazolin 3 g once within 1 hour before incision, re-dosed if surgery lasts more than 4 hours, and continued for 48 hours after surgery.
   D. Cefazolin 2 g once within 1 hour before surgery, re-dosed if surgery lasts more than 4 hours, and continued for 48 hours after surgery.

2. Which statement best describes antimicrobial stewardship in the ICU?
   A. Formal antimicrobial stewardship team membership should be reserved for clinical pharmacists with infectious diseases training.
   B. Antibiotic cycling is helpful in minimizing antimicrobial resistance.
   C. Daily clinical activities of a critical care pharmacist may constitute an antimicrobial stewardship effort.
   D. Antimicrobial stewardship should not be instituted in critically ill patients because restriction of antimicrobial choices may worsen outcomes.

3. A 33-year-old woman with a history of hydrocephalus since early childhood requiring placement of an internal cerebrospinal fluid (CSF) shunt, presents with a temperature of 102.8°F (39.3°C), altered mental status, and a white blood cell count of 19 x 10^3 cells/mm^3. After a computed tomography scan reveals no hydrocephalus or midline shift, a lumbar puncture is performed. Initial cell count shows elevated CSF white blood cells with a high proportion of neutrophils and low glucose. Neurosurgery is consulted for a presumed CSF shunt infection. Which empiric systemic antibiotic regimen is most appropriate?
   A. Ceftriaxone and ampicillin.
   B. Ceftriaxone and vancomycin.
   C. Piperacillin/tazobactam and tobramycin.
   D. Cefepime and vancomycin.

4. A 75-year-old man is admitted to the medical ICU from the emergency department with septic shock. He is fluid resuscitated and administered broad-spectrum antibiotics with piperacillin/tazobactam and vancomycin. On day 2 of therapy, the patient remains hemodynamically unstable, requiring norepinephrine. The patient's blood culture is positive, according to the institution's microbiology laboratory, which recently implemented rapid diagnostic tests using nanoparticle microarray technology, and the microarray results show the presence of *Escherichia coli* with the CTX-M resistance gene. Which intervention regarding the patient's antimicrobial therapy is most appropriate?
   A. Change piperacillin/tazobactam to cefepime.
   B. Add tobramycin to the current regimen.
   C. Add levofloxacin to the current regimen.
   D. Change piperacillin/tazobactam to meropenem.

5. An 81-year-old man is admitted to the medical ICU with presumed line-associated sepsis. Blood cultures are obtained that grow pan-sensitive *Enterobacter cloacae*. The patient is being treated with intravenous ceftriaxone, and the offending CVC is removed. The patient initially responds, but on day 10 of therapy, he becomes febrile, and blood cultures are re-sent. At that time, the patient was maintained on ceftriaxone because he was hemodynamically stable. Gram stain for the new blood cultures is positive for lactose-positive gram-negative bacilli. Which is the most appropriate action for this patient's antimicrobial management?
   A. Change ceftriaxone to ceftazidime.
   B. Change ceftriaxone to piperacillin/tazobactam.
   C. Change ceftriaxone to meropenem.
   D. Continue ceftriaxone alone.

6. An 86-year-old woman with a history of end-stage renal disease is admitted to the hospital with respiratory distress requiring intubation, fluid resuscitation, and hemodynamic monitoring. Bronchoalveolar lavage cultures show methicillin-resistant *Staphylococcus aureus* (MRSA). The patient is being treated with intravenous vancomycin. On day 4 of therapy, the patient develops fever, leukocytosis, and erythema around the insertion site of her tunneled dialysis catheter. Blood cultures are sent, and the dialysis catheter is removed. Gram stain from blood cultures is significant for gram-positive cocci in pairs and chains. The medical team discontinues vancomycin and approaches you to inquire about treatment options for this patient. Which agent is most appropriate for this patient?
   A. Daptomycin.
   B. Linezolid.
   C. Ceftaroline.
   D. Tigecycline.

7. A 35-year-old man is admitted to the medical ICU with respiratory distress. He has a 3-week history of cough and pleuritic chest pain that has worsened with time. Chest radiography is performed, which shows bilateral infiltrates with ground-glass opacities. The patient is HIV positive and not currently receiving

antiretroviral therapy because of nonadherence. The patient requires intubation and is receiving 40% fraction of inspired oxygen (Fio_2). His relevant laboratory values are as follows: SCr 1.0 mg/dL, $CD4^+$ count $100/mm^3$, lactate dehydrogenase (LDH) 550 IU/L, partial pressure of arterial oxygen (PaO_2) 80 mm Hg, partial pressure of arterial carbon dioxide ($PaCO_2$) 40 mm Hg, and white blood cell count (WBC) 4×10^3 cells/mm^3. The patient has a sulfa allergy and a glucose-6-phosphate dehydrogenase deficiency. In addition to adjunctive corticosteroids, which regimen for presumed *Pneumocystis jiroveci* pneumonia is most appropriate?

A. Trimethoprim/sulfamethoxazole 15–20 mg/kg intravenously, divided every 6 hours.
B. Pentamidine 4 mg/kg intravenously every 24 hours alone.
C. Primaquine 30 mg orally once daily plus clindamycin 600 mg intravenously every 8 hours alone.
D. Atovaquone 750 mg orally every 12 hours.

8. A 50-year-old woman with acute myeloid leukemia is admitted for induction therapy. During the patient's clinical course, she develops respiratory distress, for which she is admitted to the medical ICU. She is found to have neutropenic fever and is empirically treated with meropenem plus gentamicin plus vancomycin. On day 5 of empiric therapy, blood cultures are growing pan-susceptible *E. coli*. The patient's relevant laboratory values and vital signs are as follows: blood pressure 115/70 mm Hg, heart rate 84 beats/minute, temperature 101.2°F (38.4°C), and absolute neutrophil count less than 50 cells/mm^3. Which is the most appropriate antimicrobial regimen for the patient?

   A. Continue meropenem, gentamicin, and vancomycin for 14 days.
   B. Discontinue all empiric antimicrobials, and initiate ampicillin intravenously to treat until neutrophils recover.
   C. Discontinue vancomycin, and continue meropenem and gentamicin until neutrophil recovery.
   D. Add voriconazole, and continue all other antimicrobials for 14 days.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1-4
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 2, 4
    b. Task B: 8, 12, 13
    c. Task C: 1, 3, 4
3. Domain 3: Professional Practice
    a. Task A: 3, 4
    b. Task B: 1

I. QUALITY IMPROVEMENTS

A. The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) provides general best-practice guidelines. ACS NSQIP also provides a surgical risk calculator that, depending on the type of surgery and the patient's baseline characteristics, can generate estimated risks of complications, which include pneumonia, cardiac complications, surgical site infections (SSIs), urinary tract infections (UTIs), venous thromboembolism, renal failure, discharge to a rehabilitation facility, and death. (This risk calculator can be found at http://riskcalculator.facs.org/.)

B. As of 2016, all Surgical Care Improvement Project (SCIP) measures have been retired because of consistently high compliance rates. SCIP measure reporting is no longer mandatory. However, the practices described within the retired SCIP measures still represent best practices and should be continued. These include administration of an appropriate prophylactic antimicrobial within 1 hour of incision, discontinuation of the prophylactic antibiotic within a specified time, control of post–cardiac surgery serum blood glucose, and removal of the urinary catheter by postoperative day 2.

C. Sepsis Bundle Project (SEP-1): Specifics regarding early broad-spectrum antimicrobial administration in the management of severe sepsis and septic shock can be found in the Shock chapter.

D. Prevention of SSIs
  1. Epidemiology and clinical significance
    a. More than 110,000 SSI cases occur each year.
    b. Mortality rate is 2–11 times higher in patients who experience SSIs than in those who do not.
    c. SSIs account for \$4–\$10 billion in direct costs and can extend hospital length of stay (LOS) by 9.7 days.
  2. Classification of SSI
    a. Superficial incisional: Infection involving only the skin or subcutaneous tissue of the incision
    b. Deep incisional: Infection involving fascia and/or muscular layers
      i. Deep incision primary: Wound infection in the primary incision in a patient who has had an operation with 1 or more incisions
      ii. Deep incision secondary: Wound infection in a secondary incision in a patient who has had an operation with more than 1 incision
    c. Organ or space: Infection involving any space or organ, opened or manipulated during the procedure, excluding skin incision, fascia, or muscle layers
  3. Etiology
    a. About 70% to 95% of all SSIs arise from the microbiome of the patient's skin or nares.
    b. Prevalence of drug-resistant strains (e.g., MRSA, multidrug-resistant gram-negative bacilli) depends on the local patterns of infection and patient colonization.
      i. The most common bacterial pathogens causing SSI are *S aureus*, coagulase-negative staphylococci, *Streptococci* spp, *Enterococcus* spp, and *E coli*. Exogenous bacteria (introduced by members of the surgical team, the operating room environment, instruments, and materials brought into the sterile field) include *Staphylococci* and *Streptococci*.
      ii. Bacterial pathogens related to anatomic location of the operation:
        (a) Upper GI tract (gastric, biliary, proximal small intestine):
          (1) Biliary: Aerobic and anaerobic gram-negative bacilli and gram-positive organisms
          (2) Non-biliary: Enteric, aerobic gram-negative bacilli
        (b) Lower GI tract (distal small bowel; colon): Mixed gram-positive and gram-negative flora, facultative and anaerobic
        (c) Female genitalia: Mixed gram-positive and gram-negative flora, facultative and anaerobic
        (d) Axilla: Aerobic gram-negative organisms

            (e) Perineum: Aerobic gram-negative and mixed anaerobic organisms
            (f) Respiratory: Aerobic gram-positive and gram-negative organisms

4. Risk factors for SSIs:
    a. Patient-related factors
        i. Nonmodifiable
            (a) Advanced age
            (b) History of skin and soft tissue infection
            (c) Recent radiation
        ii. ii. Modifiable
            (a) Anticoagulation
            (b) Current tobacco use
            (c) Diabetes
            (d) Hypoalbuminemia (preoperative albumin less than 3.5 mg/dL)
            (e) Immunosuppression
            (f) Obesity
            (g) Preoperative infections
            (h) *S aureus* nasal colonization
    b. Procedure-related factors
        i. Inadequate ventilation/airborne contamination
        ii. Blood transfusions
        iii. Decreased tissue oxygenation
        iv. Presence of foreign material
        v. Longer operative time
        vi. Perioperative hypothermia
        vii. Postoperative hyperglycemia
        viii. Poor wound care
        ix. Wound contamination from patient and/or operating room personnel
        x. Inadequate skin preparation
5. Prevention strategies: Pharmacy specific
    a. Using evidence-based guidelines can prevent up to 60% of postoperative wound infections. Wound infections after elective operations are considered preventable and are reportable health care–associated infections.
    b. Many organizations and agencies promote prevention and have guidance on the prevention of SSIs, including the CDC, SCIP, The Joint Commission (TJC), Centers for Medicare & Medicaid Services (CMS), Society of Healthcare Epidemiology of America (SHEA), WHO, American College of Surgeons (ACS), and Surgical Infection Society (SIS).
        i. CMS no longer provides reimbursement to providers for the treatment of SSIs after cardiac, bariatric, orthopedic surgical procedures
    c. Preoperative
        i. Control serum blood glucose in patients with diabetes (goal blood glucose 110-150 mg/dL).
        ii. Administer prophylactic antibiotics within 1 hour before surgery (vancomycin and fluoroquinolones should be administered within 2 hours before surgery because of prolonged infusion times).
        iii. Select the appropriate prophylaxis – See Table 1.
            (a) 10%–15% of the U.S. population report an allergy to penicillin antibiotics and 1%–2% to cephalosporin antibiotics; these allergy labels often result in avoidance of cefazolin and use of alternative antibiotics (e.g., vancomycin, clindamycin).

        - (b) Retrospective cohort studies have found that patients with a reported penicillin or cephalosporin allergy had a higher odds of developing an SSI than those without a reported allergy.
        - (c) Of note, cefazolin has a unique side chain and therefore has very low cross-reactivity with penicillin. The 2022 drug allergy practice parameter update states that in patients with a history of anaphylaxis to penicillin, a structurally dissimilar R1 side chain cephalosporin (e.g., cefazolin) can be administered routinely without prior testing (*J Allergy Clin Immunol*. 2022;150(6):1333-1393).
    - iv. Adjust dose of antibiotics for obesity – See Table 2 for suggested dosing.
    - v. Patients with known nasal carriage of *S. aureus* should receive intranasal applications of mupirocin 2% ointment twice daily for up to 5 days before surgery with or without a combination of chlorhexidine gluconate body wash.
    - vi. Alcohol-based antiseptic solutions with chlorhexidine gluconate for surgical site skin preparation should be used in patients undergoing surgical procedures.
    - vii. Preoperative bowel preparation
        - (a) Although unaddressed by the CDC, preoperative bowel preparation before colorectal surgery was recommended by the ACS/SIS and WHO guidelines.
        - (b) A recent meta-analysis demonstrated that combined oral antibiotic prophylaxis combined with mechanical bowel preparation was associated with reduced SSI rates compared with mechanical bowel preparation alone. Oral antibiotic prophylaxis was associated with significant decreases in rates of anastomotic leak and 30-day mortality without increasing rates of *Clostridioides difficile* infections.
        - (c) Combined bowel preparation with oral antibiotic prophylaxis and mechanical bowel preparation is recommended by the 2019 American Society of Colon and Rectal Surgeons Clinical Practice Guidelines.
- d. Intraoperative
    - i. Re-dose antibiotics, if necessary – See Table 2 for dosing schedule during surgery.
    - ii. In general, antibiotics with short half-lives should be re-dosed at a frequency of 2 times the half-life of the agent. Antibiotics should also be re-dosed if there is significant intraoperative blood loss.
    - iii. Goal of re-dosing is to maintain bactericidal concentrations throughout the operation. It may be prudent to consider re-dosing prophylaxis intraoperatively if large amounts of fluids and/or transfusions are being administered.
    - iv. Maintain normothermia. Two small randomized controlled trials showed that maintaining normothermia reduced the risk of SSIs. The mechanism for this protective effect is currently unknown; however, a hypothesis is that this effect may result from impaired neutrophil function or subcutaneous vasoconstriction and subsequent tissue hypoxia with hypothermia.
- e. Postoperative
    - i. Discontinue prophylactic antibiotics within 24 hours after non-cardiac surgery and within 48 hours after cardiac surgery. Drains are not a sufficient reason to continue prophylactic antibiotics.
    - ii. Early recovery after surgery (ERAS) protocols: Aim to reduce the stress of surgery on patients by maintaining near normal physiology in the preoperative, intraoperative, and postoperative phases of care.
        - (a) Early recovery after surgery protocols incorporate SSI prevention guideline recommendations, such as parenteral antibiotic prophylaxis and strict glycemic control, as well as interventions with newer evidence, such as oral antibiotic prophylaxis with mechanical bowel preparation, goal directed fluid therapy, and early enteral feeding.
        - (b) A meta-analysis of 27 randomized controlled trials assessing 3279 patients undergoing abdominal/pelvic surgery showed a significant reduction in postoperative SSI for patients enrolled in ERAS pathways compared with conventional perioperative pathways.

6. Diagnosis, management, and treatment of SSIs: See Infectious Diseases I chapter.

Table 1. Prophylactic Antibiotic Regimens for Surgery

Type of Surgery	Recommended Prophylaxis	Alternative Prophylaxis in Patients with β-Lactam Allergies
Coronary artery bypass grafting Other cardiac surgery Vascular surgery Hip arthroplasty Knee arthroplasty Neurosurgery	Cefazolin Cefuroxime	Vancomycin Clindamycin
Thoracic surgery	Cefazolin Ampicillin/sulbactam	Vancomycin Clindamycin
Gastroduodenal surgery	Cefazolin	Clindamycin *or* vancomycin + aminoglycoside *or* fluoroquinolone *or* aztreonam
Colorectal surgery	Cefotetan *or* cefoxitin or ampicillin/sulbactam *or* ertapenem Metronidazole + cefazolin *or* cefuroxime *or* ceftriaxone	Clindamycin + aminoglycoside *or* fluoroquinolone *or* aztreonam Metronidazole + aminoglycoside *or* fluoroquinolone
Abdominal hysterectomy Vaginal hysterectomy Biliary tract surgery	Cefotetan *or* cefoxitin *or* ampicillin/sulbactam	Clindamycin *or* vancomycin + aminoglycoside *or* fluoroquinolone or aztreonam Metronidazole + aminoglycoside *or* fluoroquinolone

Table 2. Recommended Dose and Dosing Interval for Commonly Used Antibiotics for Surgical Prophylaxis

Antimicrobial	Recommended Dose in Adults	Dosing Interval (hr)[a]
Ampicillin/sulbactam	3 g	2
Ampicillin	2 g	2
Aztreonam	2 g	4
Cefazolin	2 g, 3 g for patients weighing ≥ 120 kg	4
Cefuroxime	1.5 g	4
Cefoxitin	2 g	2
Cefotetan	2 g	6
Ceftriaxone	2 g	N/A[b]
Ciprofloxacin	400 mg	N/A[b]
Clindamycin	900 mg	6
Ertapenem	1 g	N/A[b]
Gentamicin	5 mg/kg of ideal or adjusted body weight[c]	N/A[b]
Levofloxacin	500 mg	N/A[b]
Metronidazole	500 mg	N/A[b]
Vancomycin	15 mg/kg	N/A[b]

[a] With presumed normal renal function and dose as needed

[b] One dose of the antibiotic should suffice for the duration of most surgical procedures.

[c] Use adjusted body weight if actual body weight is > 20% of ideal body weight (IBW). Adjusted body weight = IBW + 0.4 (actual weight − IBW).

N/A = not applicable.

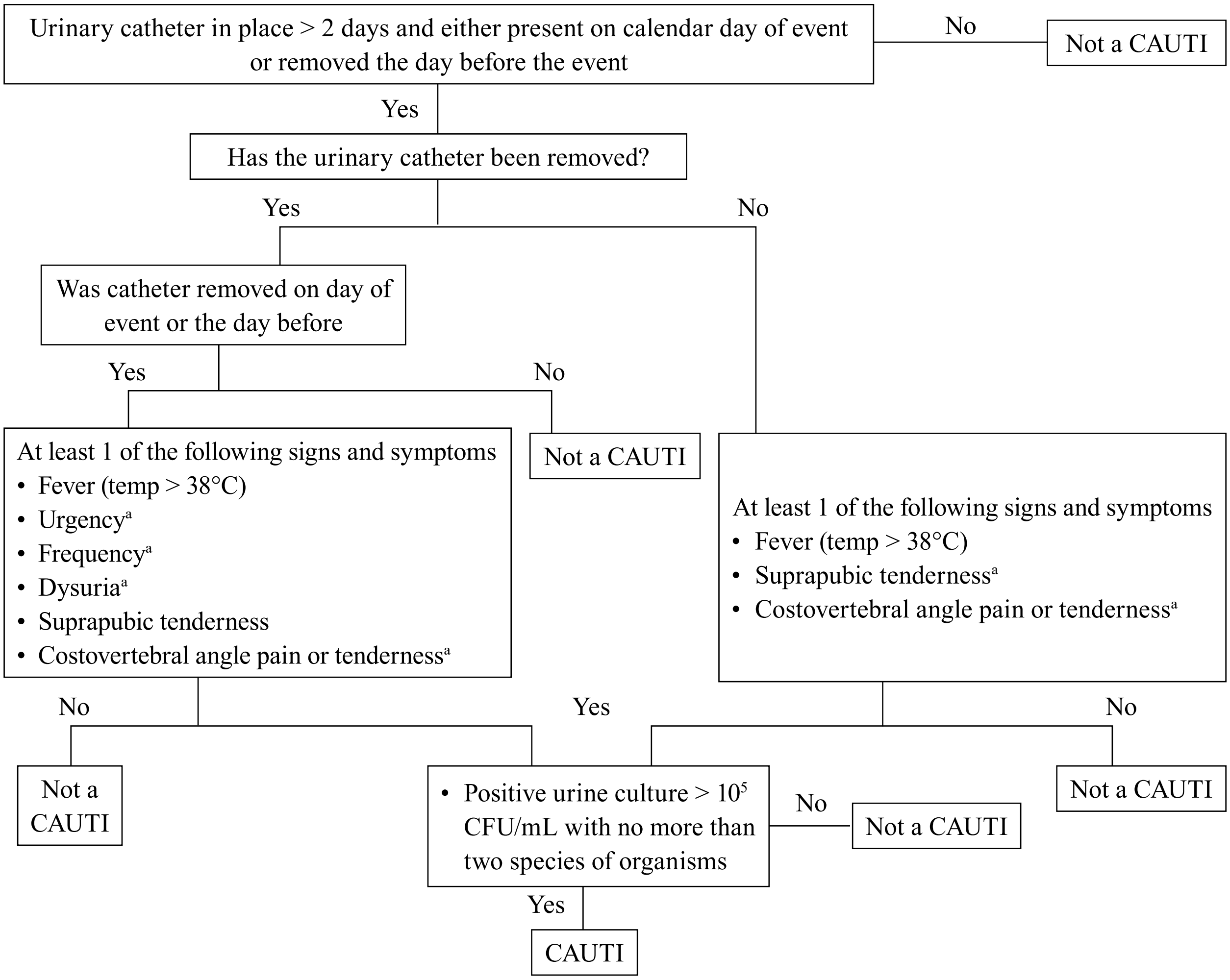
Urinary catheter in place > 2 days and either present on calendar day of event or removed the day before the event
No
Not a CAUTI
Yes
Has the urinary catheter been removed?
Yes
No
Was catheter removed on day of event or the day before
Yes
No
At least 1 of the following signs and symptoms
• Fever (temp > 38°C)
• Urgency[a]
• Frequency[a]
• Dysuria[a]
• Suprapubic tenderness
• Costovertebral angle pain or tenderness[a]
Not a CAUTI
At least 1 of the following signs and symptoms
• Fever (temp > 38°C)
• Suprapubic tenderness[a]
• Costovertebral angle pain or tenderness[a]
No
Yes
No
Not a CAUTI
• Positive urine culture > 10^5 CFU/mL with no more than two species of organisms
No
Not a CAUTI
Not a CAUTI
Yes
CAUTI

Figure 1. Diagnosis of catheter-associated urinary tract infection according to CDC criteria.

[a]With no other recognized cause

CAUTI = catheter-associated urinary tract infection.

E. Prevention of Catheter-Associated Urinary Tract Infections (CAUTIs)
   1. Definition
      a. CDC definition: See Figure 1.
      b. IDSA definition
         i. Asymptomatic bacteriuria: Refers to bacteria growing in the urine (greater than 10^5 CFU/mL) without signs and symptoms associated with UTIs
         ii. Catheter-associated symptomatic bacteriuria: In patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization (or condom catheter in a man), defined by the presence of 10^5 CFU/mL or greater of 1 or more bacterial species in a single catheter urine specimen in a patient without symptoms compatible with a UTI

      iii. CAUTI: In patients with indwelling urethral, indwelling subrapubic, or intermittent catheterization, CAUTI is defined by the presence of symptoms or signs compatible with a UTI with no other identified source of infection, together with 10^3 CFU/mL or more of 1 bacterial species in a single catheter urine specimen or in a midstream-voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours. Lower colony counts are more likely to represent significant bacteriuria in a symptomatic person than in an asymptomatic person.

2. Epidemiology and clinical significance. UTIs represent 30%–40% of all nosocomial infections.
   a. Up to 80% of UTIs are caused by urinary catheterization.
   b. More than 5% of postoperative patients will experience a UTI.
   c. CAUTIs account for $300–$400 million in additional health care costs per year.
   d. CAUTI is considered a preventable complication. CMS no longer provides reimbursement to providers for the treatment of CAUTIs.
3. Etiology
   a. Most pathogens causing CAUTIs are acquired from the external environment, including the urethra, the catheter collection system, and local skin flora. Most short-term CAUTIs are monomicrobial. Longer duration of an indwelling catheter is associated with the formation of biofilms within the catheter and related system, which can promote polymicrobial infections.
   b. *E coli* is the most prevalent pathogen causing CAUTIs; however, *E coli* accounts for only about one-third of CAUTIs. Additional bacterial pathogens include other enteric gram-negative bacilli (e.g., *Klebsiella* spp; *Proteus* spp; *Enterobacter* spp); non–lactose-fermenting, gram-negative bacilli (e.g., *P aeruginosa*); and gram-positive cocci (e.g., *Enterococcus spp*; methicillin-susceptible *S aureus* [MSSA]; MRSA; methicillin-resistant *Staphylococcus epidermidis* [MRSE]). *Candida* spp may be involved in up to one-third of CAUTIs.
   c. Similar to other health care–associated infections, causative pathogens are associated with local pathogen patterns, pathogen-specific risk factors, and patient severity of illness.
4. Risk factors: Not maintaining a closed drainage system, female sex, increased duration of catheterization, and older age
5. Prevention strategies
   a. The most effective way to reduce the incidence of catheter-associated bacteriuria and CAUTI is to minimize the use of urinary catheters by restricting their use to patients who have a clear indication and by removing the catheter as soon as it is no longer needed. In addition, urinary catheters should be removed within 24 hours postoperatively, if possible.
   b. The foundation for preventing CAUTIs includes training and education, proper aseptic insertion techniques, and active surveillance and performance improvement systems.
      i. Pharmacists may provide reminders as part of a multidisciplinary effort to minimize the placement and duration of urinary catheters.
   c. Recommended best practices for preventing CAUTIs have been proposed and endorsed by IDSA, SHEA, CDC, and TJC. These evidence-based recommendations are categorized as essential practices for all acute care hospitals. The entire document is available at *Infect Control Hosp Epidemiol.* 2023;44(8):1209-1231. Major recommendations include:
      i. Essential practices
         (a) Insert urinary catheters only when necessary for patient care, and leave in place only as long as indications remain.
         (b) Provide comprehensive education to and ensure competency for all involved with insertion, care, and maintenance of urinary catheters.
         (c) Use a systematic process or checklist at the time of insertion to ensure adherence to proper insertion technique.

        - (d) Practice hand hygiene before insertion of the catheter, as well as before and after any manipulation of the catheter site or apparatus.
        - (e) Proper care and maintenance of indwelling catheter and collection system
    - ii. Additional approaches
        - (a) Establish a system for analyzing and reporting data on catheter use.
        - (b) Develop and implement a protocol to manage postoperative urinary retention.
- d. Strategies that should NOT be considered (all of these practices have low-quality evidence suggesting no benefits in preventing CAUTIs):
    - i. Routine use of silver or antibiotic-impregnated catheters. According to the CDC, silver or antibiotic-impregnated catheters can be considered if a comprehensive strategy to reduce CAUTI rates has failed. The ACS NSQIP best-practices guidelines suggest that use of antimicrobial urinary catheters can be considered for high-risk patients, such as those who may require prolonged (greater than 7–10 days) catheterization.
    - ii. Addition of antibiotics to drainage bag
    - iii. Use of systemic antibiotic prophylaxis solely due to catheter placement
    - iv. Routine screening or treatment of asymptomatic bacteriuria
    - v. Bladder irrigation with antibiotics

6. Diagnosis, management, and treatment of CAUTIs: See Infectious Diseases I chapter.

Patient Case

1. C.L is a 55-year-old man admitted to the surgical ICU after exploratory laparotomy for duodenal perforation and peritonitis. The patient was transferred from the operating room to the surgical ICU with a urinary catheter in place. On day 4 of the surgical ICU stay, the patient is extubated, and his urinary catheter is removed. On day 6 of the surgical ICU stay, the patient develops signs and symptoms of UTI with fever, urgency, and frequency. Urinalysis reveals no nitrites or leukocyte esterase. Urine cultures show 100,000 CFU/mL of *E. coli*. You are asked by the quality officer of the surgical ICU to discuss this case and determine whether this patient will qualify for the definition of CAUTI according to CDC criteria. Which statement regarding the diagnosis of CAUTI in this patient is most appropriate?

    A. Qualifies for definition of CAUTI because the patient is symptomatic and has positive cultures.
    B. Does not qualify for definition of CAUTI because the patient had a negative urinalysis.
    C. Qualifies for definition of CAUTI because the patient is symptomatic and had recent urinary catheter.
    D. Does not qualify for definition of CAUTI because the catheter was removed 2 days before symptoms.

F. Prevention of Catheter-Related Bloodstream Infections

1. Definitions
    - a. CDC definition: Must satisfy both criteria
        - i. Laboratory-confirmed bloodstream infection
            - (a) Definition 1: A recognized pathogen (not a common skin contaminant) found in one or more blood cultures AND the organism is not related to an infection at a separate site
            - (b) Definition 2: At least one sign or symptom of infection (temperature greater than 100.4°F [38°C], chills, hypotension) AND a common skin flora is cultured from two or more blood samples AND organism is not related to an infection at a separate site
        - ii. Central line placed for more than 2 days before the date of event and central line must be present or removed within 24 hours of blood cultures being obtained.

- b. IDSA definition: Defines catheter-related bloodstream infection minimally as bacteremia or fungemia in a patient who has an intravascular device and:
    - i. More than 1 positive blood culture obtained from a peripheral vein. A definitive diagnosis requires that the same organism or organisms grow from at least 1 percutaneous blood culture and from the CVC tip or that 2 blood cultures, 1 from a catheter hub and 1 from a peripheral vein, be positive for the same organism(s);
    - ii. Clinical manifestations of infection (e.g., fever, chills, and/or hypotension); and
    - iii. No apparent source for bloodstream infection other than the catheter.

2. Epidemiology and clinical significance
    - a. In 2012, the National Healthcare Safety Network (NHSN) reported central line–associated bloodstream infection (CLABSI) rates across adult critically ill patient populations of 0.8 to 3.4 episodes per 1000 central line–days. Aggregated national data from 2016 showed almost a 50% decrease in CLABSI rates from 2008 (0.56-1.00 cases per 1000 central line–days). Although specific rates vary between sites and populations, all central line types and locations of insertion have an attributable risk of bloodstream infection.
    - b. Accounts for 14,000–28,000 deaths per year
    - c. Increases mean LOS by 7 days
    - d. CLABSI is considered a preventable complication. The NHSN, using CDC definitions, provides population-specific event rates for institution surveillance and performance benchmarks. CMS no longer provides reimbursement to providers for the treatment of catheter-related bloodstream infections.
3. Etiology
    - a. CLABSIs are usually monomicrobial. Pathogen prevalence is based on patient-specific risk factors and underlying illness.
    - b. Common organisms responsible for CLABSIs include coagulase-negative staphylococci (e.g., *S epidermidis*), *S aureus*, *Candida* spp, and enteric gram-negative bacilli (e.g., *E coli*, *Klebsiella* spp, *Enterobacter* spp).
    - c. Risk factors for multidrug-resistant organisms include critical illness, femoral catheter placement, immunosuppression, and previous antibiotic exposure.
    - d. *Candida* spp are more common in patients with the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, stem cell or solid-organ transplantation, femoral catheterization, or colonization owing to *Candida* spp at several sites.
4. Risk factors
    - a. Patient factors: Diabetes, hypotension, male sex, neutropenia, parenteral nutrition, prolonged hospitalization before catheter placement
    - b. Catheter-related factors: Heavy microbial colonization at insertion site, inadequate catheter care, internal jugular or femoral vein placement site (compared with subclavian vein), prolonged duration of venous catheterization, use of non-tunneled catheters
5. Prevention strategies
    - a. Updated recommendations for best practices in the prevention of CLABSI have been sponsored by SHEA, IDSA, the Association for Professionals in Infection Control, the American Hospital Association, and TJC. These updates include evidence-based recommendations categorized as essential practices that should be adopted by all acute care hospitals, or additional approaches that can be considered for use in locations and/or populations within hospitals when CLABSIs are not controlled after implementation of essential practices (*Infect Control Hosp Epidemiol.* 2022;43(5):553-569).
        - i. Essential practices
            - (a) Minimize central venous line insertions and durations of insertion.
            - (b) Provide comprehensive education to ensure competency for all involved with insertion, care, and maintenance of CVCs.

        - (c) Daily chlorhexidine baths for patients to reduce colonization
        - (d) Use of a systemic process or checklist at the time of insertion to ensure adherence to the proper insertion technique
        - (e) Alcohol-based chlorhexidine skin cleanser for skin preparation
        - (f) Perform hand hygiene during insertion, care, and maintenance of the catheter.
        - (g) Cleanse catheter hubs before accessing.
        - (h) Routine post-insertion site care
        - (i) Routine replacement of administration sets not used for blood, blood products, or lipid formulations can be performed at intervals up to 7 days.
        - (j) Chlorhexidine-containing site/catheter dressings
      - ii. Additional approaches
        - (a) Use antiseptic or antimicrobial-impregnated catheters.
        - (b) Use antimicrobial ointments for hemodialysis catheter insertion sites.
        - (c) Use antiseptic hub cover or port protector.
        - (d) Antimicrobial lock therapy
        - (e) Use recombinant tissue plasminogen activating factor weekly if dialysis is performed through CVC.
    - b. Use appropriate techniques for catheter insertion (e.g., skin preparation and maximal sterile barrier precautions) and management (e.g., daily site care, routine site evaluation for local erythema). Minimize the use of CVCs. Pharmacists may provide reminders as part of a multidisciplinary effort to minimize the placement and duration of venous catheters.
    - c. Consider antibiotic lock therapy in patients with limited venous access or a history of catheter-related bloodstream infections.
    - d. Do not use systemic antibiotic prophylaxis.
    - e. Antimicrobial/silver-impregnated catheter should be considered in patients with an anticipated catheter duration greater than 5 days if rates of catheter-related bloodstream infections have not decreased despite the implementation of a comprehensive prevention strategy.
  - 6. Diagnosis, management, and treatment of CLABSIs: See Infectious Diseases I chapter.

II. BACTERIAL MENINGITIS

- A. Definitions
  1. Bacterial meningitis is a neurologic emergency involving mild to severe inflammation of the meningeal layers encasing the central nervous system (CNS). Cerebrospinal fluid (CSF) is intimate to the meninges and serves as both a medium for pathogen growth and a diagnostic fluid.
  2. Community-acquired meningitis is an infection unrelated to a neurosurgical procedure, neurotrauma, or hospitalization.
  3. Health care–associated or nosocomial meningitis is an infection related to invasive procedures, including craniotomy, internal or external ventricular catheters, lumbar puncture, intrathecal medication administration, and/or spinal anesthesia. Additional causes include complicated cranial trauma, traumatic brain injury, and hematogenous spread in patients with hospital-acquired bacteremia.

B. Epidemiology
  1. Bacterial meningitis has community-acquired or health care–associated epidemiology; health care–associated meningitis is usually associated with neurotrauma or neurosurgical procedures.
  2. Community-acquired bacterial meningitis has an annual incidence in adults of about two cases per 100,000 people. The incidence has been decreasing, likely because of increased vaccination against common pathogens. The incidence of nosocomial bacterial meningitis varies depending on the mechanism of neuro-anatomic disruption and ranges from 1.5% of patients undergoing craniotomy to 25% of post-trauma patients with basilar skull fracture.
  3. Delayed CSF sterilization beyond 24 hours is a risk factor for subsequent neurologic sequelae, including intracranial hypertension, seizures, and permanent neurologic deficit. Clinical presentations of septic shock, altered mental status, and seizures are associated with worse outcomes. Additional complications include respiratory failure and hyponatremia.
  4. Crude mortality for community-acquired meningitis is 19%–37%, whereas mortality for health care–associated meningitis is generally lower, particularly if associated with a reversible procedure or removable device.

C. Diagnosis
  1. The clinical diagnosis of meningitis is nonspecific and difficult to distinguish from that of other infections. Although headache, fever, neck stiffness, and altered mental status are present in almost 95% of patients with community-acquired meningitis, fever and a decreased level of consciousness are the most consistent clinical features in patients with health care–associated meningitis.
  2. Lumbar puncture or other method (e.g., from existing drain or shunt) to sample CSF for cell count and analysis, as well as Gram stain and culture, is necessary for definitive diagnosis. Neuroimaging with head computed tomography to detect prelumbar brain shift and risk of brain herniation should be done before lumbar puncture in patients with suspected cranial mass (e.g., immunosuppressed, papilledema, history of CNS disease, new-onset seizure, and focal neurologic deficit).
    a. Opening pressure during lumbar puncture is usually increased in bacterial meningitis; it is usually in the range of 200 to 500 cm H_2O (normal opening pressure in adults: 10–20 cm H_2O).
    b. Cell count and fluid analysis
      i. Community-acquired bacterial meningitis can be differentiated from other causes of meningitis (e.g., viral, aseptic). In general, bacterial meningitis is associated with CSF that is predominantly neutrophilic and has lower glucose concentration. Strong predictors of bacterial meningitis include:
        (a) CSF glucose less than 40 mg/dL
        (b) Ratio of CSF to blood glucose less than 0.6
        (c) CSF protein greater than 220 mg/dL
        (d) CSF WBC greater than 100 to 1000 cells/μL
        (e) CSF leukocyte count greater than 2000 cells/mm^3
        (f) CSF neutrophil count greater than 1180 cells/mm^3
      ii. The diagnostic utility of CSF cell count and fluid analysis in health care–associated meningitis is unknown but is likely limited because of concomitant reasons for local inflammation related to devices or recent procedures. In the presence of CSF drains or recent history of neurosurgery, new headache, nausea, lethargy, and/or change in mental status may be a sign of new CNS infection. Neither normal CSF analysis nor negative Gram stain may exclude the presence of an infection. Elevated CSF lactate concentration may be useful to distinguish meningitis from other infectious sources.

    c. Gram stain and culture: Bacteriologic examination of CSF can provide rapid and reliable identification of the causative pathogen(s). Although CSF cell count and analysis is the diagnostic foundation for community-acquired meningitis, CSF culture is the most specific test for health care–associated meningitis. Of note, immunocompromised patients with meningitis may present with normal CSF cell counts.

D. Management and Treatment
  1. Appropriate empiric antibiotic therapy administered intravenously, targeted against likely pathogens, and guided by local antibiotic susceptibility patterns should be initiated as soon as possible after bacterial meningitis is suspected. See Table 3 for common pathogens and recommended empiric therapy.
  2. Antibiotic dosing and administration strategies should be chosen to optimize CSF concentrations relative to bacterial minimum inhibitory concentration (MIC) and antibiotic pharmacodynamic (PD) properties. Although meningeal inflammation may promote CSF penetration, data are inconsistent regarding its impact on effective antimicrobial delivery. Furthermore, as meningitis improves, inflammation will likely improve, and there is currently no way to predict the level of penetration in correspondence to the severity of the inflammation.
  3. Gram stain can be used to broaden bacterial coverage, but final culture should be reserved for antibiotic de-escalation and definitive antibiotic regimen.
  4. Role of corticosteroids
     a. Adjunctive corticosteroids may improve outcomes by reducing reactive meningeal inflammation and neurologic sequelae related to antibiotic-induced bacterial lysis.
     b. Conflicting results are published regarding the effects of systemic corticosteroids on neurologic sequelae and mortality among patients with bacterial meningitis.
     c. Studies from high-income countries tend to suggest that systemic corticosteroids decrease or trend toward a decrease in mortality and neurologic sequelae.
     d. The outcome benefit associated with systemic corticosteroids seems most pronounced in patients with *Streptococcus pneumoniae* meningitis. However, because corticosteroids must be administered before the receipt of antimicrobials, it is unlikely that clinicians will know the etiology of the disease when making the decision for steroids.
     e. The IDSA guidelines recommend administering dexamethasone 0.15 mg/kg every 6 hours for up to 96 hours, with the first dose administered 10–20 minutes before, or at least concomitant with, the first dose of antimicrobial therapy. The IDSA guidelines also recommend continuation of dexamethasone only if cultures show the presence of *S. pneumoniae*, although this recommendation is not supported by strong clinical evidence.
  5. Health care–associated meningitis
     a. See Table 3 for recommended empiric treatment of health care–associated meningitis.
     b. In patients with CSF shunts, complete removal of an infected CSF shunt and replacement with an external ventricular drain combined with intravenous antimicrobial therapy is recommended.
     c. In selected patients with bacterial meningitis after placing a CSF shunt, the IDSA recommends direct instillation of antimicrobial agents intraventricularly through either an external ventriculostomy or shunt reservoir. This practice should only be considered in patients with pathogens that are difficult to eradicate or for those who cannot undergo catheter replacement. See Table 4 for selected antimicrobial intraventricular dosing. When intraventricular antibiotics are administered, drains should be clamped for 15-60 minutes to allow antibiotics to equilibrate throughout the CSF. Antimicrobial agents administered into the CNS should be preservative free. Dosing and intervals of intraventricular antimicrobial therapy should be adjusted on the basis of the CSF antimicrobial concentration being 10-20 times the MIC of the causative pathogen, ventricular size, and daily output from ventricular drain. Given the paucity of pharmacokinetic (PK) data

surrounding intraventricular antibiotics administration and the lack of head-to-head comparisons with intravenous antimicrobials, the administration of systemic antimicrobials should be continued in conjunction with intraventricular antibiotics.

6. Definitive antibiotic therapy can be determined according to finalized cultures and susceptibility results. In general, definitive therapy should entail choosing the therapy with the most appropriate spectrum of activity and an adequate penetration into the CSF. Therapy should be continued for at least 7 days in all patients with meningitis. *S. pneumoniae*, coagulase-negative staphylococci, *S. aureus*, gram-negative bacilli, and *Cutibacterium acnes* (previously known as *Propionibacterium acnes*) should be treated for 10–14 days and *Listeria monocytogenes* for at least 21 days. CSF should be negative for *S. aureus* for at least 10 days before shunt replacement.

Table 3. Common Pathogens Seen in Different Bacterial Meningitis Populations and the Corresponding Recommended Empiric Therapy

Patient Group	Common Pathogens	Recommended Empiric Therapy
Community-Acquired Pathogens		
18–50 yr	*N. meningitidis*, *S. pneumoniae*	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone)
> 50 yr *or* any age with predisposing condition[a]	*N. meningitidis*, *S. pneumoniae*, *L. monocytogenes, H. influenzae,* aerobic GNB (e.g., *E. coli)*	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone) + ampicillin
Health care–associated or nosocomial		
Basilar skull fracture (communication with sinuses or oropharynx)	*S. pneumoniae*; *H. influenzae*; group A β-hemolytic streptococci	Vancomycin + third-generation cephalosporin (e.g., ceftriaxone)
Penetrating trauma	*S. aureus*, CoNS, aerobic enteric (e.g., *E. coli*) and non–lactose-fermenting (e.g., *P. aeruginosa*) gram-negative bacilli	Vancomycin + cefepime *or* ceftazidime *or* meropenem
Post-neurosurgery	Aerobic enteric (e.g., *E. coli*) and non–lactose-fermenting (e.g., *P. aeruginosa*) gram-negative bacilli, *S. aureus*, CoNS	Vancomycin + cefepime *or* ceftazidime *or* meropenem
CSF shunt	Aerobic enteric (e.g., *E. coli*) and non–lactose-fermenting (e.g., *P. aeruginosa*) gram-negative bacilli, *S. aureus*, *Propionibacterium acnes*	Vancomycin + cefepime *or* ceftazidime *or* meropenem

[a] Altered immune status, alcoholism

CoNS = coagulase-negative staphylococci; GNB = gram-negative bacteria.

Table 4. Selected Antibiotic CSF Penetration and Dosages for Meningitis

Agent	CSF Penetration, % of Serum Concentration	Dosage for Meningitis
Amikacin	Low	Conventional: 10–15 mg/kg[a] IV q8–12hr Extended interval: 20–25 mg/kg[a] IV once daily Intraventricular: 30 mg once daily
Ampicillin	13–14	2 g IV q4hr
Cefazolin	8–15	2 g IV q8hr
Cefepime	10–20	2 g IV q8hr
Cefotaxime	10–12	2 g IV q4hr
Ceftazidime	30–40	2 g IV q8hr
Ceftriaxone	8–12	2 g IV q12hr
Ciprofloxacin	20–25	400 mg IV q8hr
Colistin	Low	Intraventricular: 10 mg once daily
Meropenem	6–21	2 g IV q8hr (extended infusions over 3 hr may be considered)
Nafcillin	1–2.5	2 g IV q4hr
Piperacillin/tazobactam	20–30	Not recommended because of low penetration of tazobactam
Tobramycin	10–20	Conventional 2–3 mg/kg IV q8–12hr Extended interval: 5–7 mg/kg IV once daily Intraventricular 10–20 mg once daily
Vancomycin	30	15–20 mg/kg IV q8–12hr Intraventricular 10–20 mg once daily

[a] Use IBW unless actual body weight is > 20% of IBW. If actual body weight is >20% IBW use adjusted body weight. Adjusted body weight = IBW + 0.4 (actual weight − IBW).

IV = intravenous(ly); q = every

Patient Case

2. H.K. is a 42-year-old woman who presents with her husband to the emergency department from home with mental status changes, lethargy, and a temperature of 102.9°F (39.4°C). Her husband reports that she had a severe headache 24 hours earlier. She has no significant medical history. Diagnostic workup results are highly suggestive of meningitis. A lumbar puncture is performed, during which a high initial pressure is noted. Which intervention would be best initially for H.K.?

   A. Administer dexamethasone 0.15 mg/kg intravenously.
   B. Await laboratory and microbiologic analysis.
   C. Initiate empiric ceftriaxone and vancomycin.
   D. Initiate empiric ampicillin, cefepime, and vancomycin.

III. ANTIBIOTIC STEWARDSHIP

A. Goals: To optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, which include the emergence of antimicrobial resistance and adverse drug reactions. In addition, a responsible approach to the use of antimicrobial agents should reduce the overall costs associated with treatment.

  1. Antibiotics are the second most common class of drugs that cause adverse effects.
  2. Antibiotics are the most common class of medication to be associated with prescribing errors.
  3. Minimizing antimicrobial resistance by optimizing therapy should lead to measurable benefits at the patient level because studies have shown the negative effect of antimicrobial resistance on several clinical outcomes.
  4. Effective January 2017, TJC announced a new medication management standard that addresses antimicrobial stewardship. Many of the standards are applicable and relevant to critical care pharmacists: continuing education of staff, education of patients and family members, participation in an antimicrobial stewardship team, and development and execution of antimicrobial management protocols.
  5. In 2018, CMS finalized a rule that requires all acute care hospitals participating in Medicaid/Medicare services to implement antibiotic stewardship programs (ASPs). In 2022, additional requirements were recommended including organization and policies for infection prevention and control programs and ASPs, leadership responsibilities, and unified and integrated infection prevention and control programs and ASPs for multi-hospital systems.
  6. In 2019, the CDC updated the hospital core elements to reflect the new evidence in the field of antibiotic stewardship. Major updates include hospital leadership commitment, accountability, pharmacy expertise, tracking, reporting, and education. In 2023, TJC published new and revised elements of performance that address antibiotic stewardship. New elements of performance include allocation of financial resources for staffing and information technology to support the ASP, the requirement that ASPs monitor the hospital's antibiotic use by analyzing data on days of therapy per 1000 days present or 1000 patient-days, the recommendation that ASPs implement preauthorization for specific antibiotics and/or prospective review and feedback regarding antibiotic prescribing practices, the recommendation that ASPs implement at least 2 evidence-based guidelines to improve antibiotic use (e.g., community-acquired pneumonia, skin and soft tissue infections), and the recommendation that ASPs evaluate adherence to at least 1 of the evidence-based guidelines that the hospital implements.

B. Antibiotic Stewardship Definition: Multidisciplinary and coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents and to promote the selection of optimal antimicrobial drug regimen, including dosing, duration, and route of administration.

  1. Core members of a multidisciplinary antimicrobial stewardship team should include an infectious diseases physician, a clinical pharmacist, a clinical microbiologist, an information systems specialist, an infection control professional, a nurse, and a hospital epidemiologist.
  2. Broad-spectrum antimicrobials are often necessary in the ICU to provide early effective therapy. However, continued use of broad-spectrum antimicrobials may lead to the selection of pathogenic organisms (i.e., *C. difficile, Candida* spp.), nephrotoxicity, and the emergence of resistance.

C. Critical care pharmacists are well positioned to provide guidance on antimicrobial therapy, including expedited selection of appropriate initial agents, aggressive dosing to optimize PD, interpretation of microbiological evidence, appropriate de-escalation of antimicrobials, monitoring of response and potential adverse effects, and determination of the appropriate treatment duration

1. Critical care pharmacists could either have an active role as a member of a multidisciplinary antibiotic stewardship team or serve in many of the different roles and activities of antibiotic stewardship.
2. Core activities that can be pursued through formal pathways or everyday clinical interventions:
    a. Education with active intervention – Interpretation of rapid identification tests and susceptibility testing
    b. Guidelines and clinical pathway development. Recent IDSA guidelines recommend facility-specific clinical practice guidelines or algorithms as an effective way of standardizing prescribing practices.
    c. Streamlining or de-escalation of therapy
        i. Shortening therapy duration
        ii. Discontinuing unnecessary antimicrobials
    d. Dose optimization
        i. Application of PK/PD principles. Per IDSA recommendations, PK and dose-monitoring programs are specifically recommended for vancomycin and aminoglycosides.
        ii. Dose adjustments based on organ function
        iii. Allergy detection and assessment, in particular promotion of β-lactam skin testing when appropriate
    e. Parenteral to oral conversion
    f. Recent IDSA guidelines recommend against the use of didactic education alone for stewardship.
3. Support from microbiology laboratory and electronic medical record system surveillance and clinical decision support may further enhance stewardship efforts.

D. Antimicrobial Stewardship Strategies (can be used synergistically)
1. Prospective audit with intervention and feedback (“back-end” strategy)
    a. Allows flexibility and minimizes delay in administering therapy
    b. The most successful strategy involves direct communication with treating physicians and required documentation for acceptance of recommendation or rationale for denial.
2. Formulary restriction and preauthorization (“front-end” strategy).
    a. May be resource-intensive, and prescribers may feel a loss of autonomy
    b. Initial choices of antimicrobials may be optimized through consultation with infectious disease experts.
    c. Antimicrobial cycling: An example of formulary restriction in which there is a scheduled removal and substitution of a specific antimicrobial or an antimicrobial class. It is an effort to minimize antimicrobial selection pressures. Evidence is insufficient to suggest that antimicrobial cycling strategies are effective. IDSA stewardship guidelines recommend against the use of antimicrobial cycling as a stewardship strategy. The compensatory overuse of another class of antibiotics has been reported when attempts to restrict a different class of antibiotics were implemented.
3. Regardless of the strategies used or the quality of clinical pathways, programmatic antibiotic stewardship is not a substitute for clinical judgment.
4. Process indicators (e.g., days of therapy, provider adherence to clinical pathway, time to effective therapy) and outcome measures (e.g., LOS, mortality, 30-day readmission) should be used to gauge program success.

E. Effective ASPs Can Be Financially Self-Supporting
1. Antimicrobials can account for up to 30% of hospital pharmacy budgets, with up to 50% of antimicrobial use being inappropriate, leading to increased cost, increased selection of resistant pathogens, and increased selection of opportunistic infections (OIs).

2. Several studies have shown significant cost savings associated with ASPs. However, most of these studies focused only on antimicrobial costs, with little focus devoted to indirect costs and implementation costs.
3. There is currently a proposed CMS rule for incorporating antibiotic prescribing patterns as one of the quality-reporting metrics. Many CMS quality metrics are tied to reimbursement. If this metric becomes tied to reimbursement, there will be further incentives to implement antimicrobial stewardship programs.

F. Evidence Supporting Antibiotic Stewardship Efforts in Critically Ill Patients
   1. Studies in this area have been limited by poor study design. However, most studies have reported a decreased use in either antibiotics overall or a targeted class of antibiotics. Some studies have also reported a decrease in key resistance rates.
   2. Antimicrobial stewardship strategies used in studies have varied widely, including restriction, formal infectious disease physician consultation, protocols for de-escalation, implementation of computer-assisted decision support, and formal reassessments of the empiric antibiotics by a stewardship team.
   3. Meta-analyses of before-after studies evaluating prospective audit and feedback of ICU patients receiving antibiotics found no increase in mortality, suggesting that this practice could safely be implemented in critically ill patients.

IV. RAPID DIAGNOSTIC TESTS

A. Rationale
   1. There is an association between delay in administration of appropriate antimicrobials and decreased survival among patients with septic shock.
   2. Broad-spectrum antimicrobials are usually used in severe infections to ensure that all potential pathogens are covered.
   3. Rapid diagnostic tests may assist in de-escalation efforts in an attempt to practice antibiotic stewardship. Critical care pharmacists are advocates for the appropriate use of antimicrobials according to the results of rapid diagnostic tests.
   4. In many cases, the implementation of rapid diagnostic tests may be cost neutral, or even constitute a cost savings, when antimicrobial stewardship efforts leading to decreased consumption of antibiotics occur.
   5. Recommended by IDSA antibiotic stewardship guidelines to be used in combination with stewardship team to optimize antibiotic therapy and improve clinical outcomes
   6. The Society of Infectious Diseases Pharmacists released an official position statement stating that rapid diagnostic tests can help antimicrobial stewardship programs decrease unnecessary exposure and optimize patient care.

B. Early Pathogen Identification from Positive Bloodstream Cultures
   1. All discussed methods attempt to shorten the time from blood culture positivity to species identification or susceptibility testing. Traditional pathogen identification and susceptibility testing can take 72–96 hours. Early pathogen identification techniques seek to provide clinically actionable information within the first 24 hours from the time of culture positivity. See Table 5 for examples of rapid diagnostic tests, corresponding targets, and respective turnaround times.

2. Most of these techniques, when combined with antibiotic stewardship efforts, lead to significant reductions in health care costs and improvements in clinical outcomes in relevant studies. However, many of these were single-center studies, which makes external validity questionable. The overall impact of the implementation of rapid diagnostic tests in a single institution is determined by several factors.
    a. Epidemiology of targeted organisms
    b. Presence and actions of existing antibiotic stewardship teams
    c. Current clinician prescribing patterns
    d. Patient population
3. The inability to detect polymicrobial infections is a common limitation to most of the techniques described.
4. Newer methods using whole blood (vs. blood culture medium or agar plates) have been developed (LightCycler SeptiFast, SepsiTest).
    a. A benefit to identification from whole blood is the ability to identify bacteria in patients with recent or current antibiotic exposure.
5. Some of the technology discussed has been developed for respiratory cultures, but the clinical adaptation in that arena is considerably less than that for blood cultures.
6. Application of rapid diagnostic tests that detect genetic encoding of resistance mechanisms requires further education and guidelines to assist clinicians in choosing the proper therapy because traditional susceptibility results are not available. See Table 6 for a reasonable approach based on the detection of resistance genes and species.
7. Peptide nucleic acid (PNA) fluorescence in situ hybridization (FISH)
    a. Mechanism: Targets species-specific ribosomal RNA from positive blood cultures
    b. Sensitivity and specificity: 96%–100%
    c. Limitations: Does not provide antimicrobial sensitivity data. Currently available FISH products are only used for species identification; however, the FDA approved a new product that could detect the *mecA* gene for detecting the presence of methicillin resistance. This product is not currently commercially available.
    d. Application
        i. Separates *S. aureus* from possible skin flora contamination of coagulase-negative staphylococci (CoNS).
        ii. Differentiates *Enterococcus faecium* (which is often resistant to ampicillin and vancomycin) from *Enterococcus faecalis*.
        iii. Identifies fluconazole-sensitive *Candida* spp. for patients empirically treated with echinocandins.
        iv. Detects *Pseudomonas* versus non-*Pseudomonas* gram-negative spp. in patients treated with combination gram-negative therapy.
    e. Studies
        i. A retrospective study evaluating the outcome and economic benefit of PNA FISH methods for the early differentiation of CoNS and *S. aureus* bacteremia in clinical practice showed a significant cost savings and a decrease in median LOS. Of note, the PNA FISH results were combined with the efforts of an antibiotic therapy team. Similar results have been shown with PNA FISH implementations for other pathogens, including *Enterococcus* spp. and *Candida* spp. These results are in contrast to those of another study that evaluated the pre- and post-staphylococci PNA FISH implementation results without the use of an antibiotic stewardship team. This study found no significant effects on patient LOS or vancomycin use. This suggests that rapid identification tests are probably beneficial only when combined with educational efforts and prospective alerts to notify clinicians of the clinical applicability of the test results.

   ii. In a prospective randomized controlled study in which patients were randomized to early notification of PNA FISH results for CoNS or *S. aureus* within 3 hours or usual care, intervention was associated with decreased mortality, decreased antibiotic use, and decreased LOS. The most pronounced benefits occurred in critically ill patients.

8. Mass spectroscopy: Matrix-assisted laser desorption-ionization/time of flight (MALDI-TOF)
   a. Mechanism: Mass spectroscopy is compared with library standards for identifying pathogen species and/or resistance mechanisms. Mass spectroscopy is an analytic technique whereby samples are ionized that produces a mass spectrogram for the sample. Each sample has a unique mass spectrogram, similar to a fingerprint, which can be matched to a library of reference standards for identification.
   b. Sensitivity and specificity: 98%–100%
   c. Limitations
      i. Similar to PNA FISH, no antimicrobial susceptibility is reported; however, the technology could detect genes encoding resistance. MALDI-TOF for resistance genes is currently not commercially available.
      ii. Cannot be used for polymicrobial cultures
      iii. No library is available for unusual organisms, though pathogen libraries are consistently being updated.
   d. Application: Potentially wider clinical applicability than PNA FISH (which is limited by the availability of specific tests for certain pathogens) with early identification of many more pathogens. Additional library standards for different pathogens are continually being added.
   e. Studies: This strategy has been evaluated in several studies. In a before-and-after study of MALDI-TOF implementation, a shortened time to pathogen identification and a decrease in LOS, recurrent infections, and mortality were seen. Of note, the implementation of MALDI-TOF included communicating the results to the treating clinicians by an antibiotic stewardship team with evidence-based antibiotic recommendations.
9. Polymerase chain reaction (PCR)-based detection systems
   a. MRSA PCR test
      i. Mechanism: Novel multiplex real-time assay for *mecA* gene
      ii. Sensitivity and specificity: 85% and 92%, respectively, for MRSA and MSSA identification
      iii. Application: Earlier de-escalation of anti-MRSA antimicrobials and earlier appropriate treatment with antistaphylococcal penicillin (oxacillin, nafcillin, cefazolin) for MSSA
         (a) Most experience and evidence with using the MRSA PCR test is for de-escalation of MRSA-active antibiotics in patients with pneumonia. New evidence also shows this may be used for de-escalation in patients with intra-abdominal infections, bloodstream infections, wound cultures, and urinary cultures.
         (b) Providers may use results from MRSA PCR test for up to 14 days between specimen collections (negative predictive value at 14 days in one study was 95.5%). Another study demonstrated that MRSA nares screening within 60 days of ICU admission has a high negative predictive value (98%) and specificity (96%).
      iv. Studies: In a before-and-after study, implementation of the MRSA PCR test resulted in reduced time to appropriate therapy and duration of unnecessary MRSA coverage. In addition, the mean hospital costs were decreased, and there was a trend toward decreased LOS. In a very similar study, the combination of the MRSA PCR test with antimicrobial stewardship efforts resulted in significant decreases in LOS and cost and a trend toward decreased mortality (18% vs. 26%).
   b. FilmArray System
      i. Mechanism: Uses multiplex PCR technology to identify bacterial species and resistance genes

        - ii. Sensitivity and specificity
            - (a) For species identification: Greater than 90%
            - (b) For resistance genes: 100% (currently only available for *mecA* - methicillin resistance; van A/B - vancomycin resistance; *Klebsiella pneumoniae* carbapenemase [KPC] - carbapenem resistance)
        - iii. Application: Earlier escalation or de-escalation of antimicrobial agents
        - iv. Studies have shown an earlier time to pathogen identification and antibiotic de-escalation. One study found no difference in mortality, LOS, or cost when multiplex PCR was combined with antibiotic stewardship.

10. Nanoparticles (Microarray): Verigene blood culture test
    - a. Mechanism
        - i. Direct detection from positive blood culture medium using nanoparticle technology
        - ii. Nucleic acid extraction and array hybridization
    - b. Most-developed commercially available product with resistance gene detection
    - c. Sensitivity and specificity: 93%–100%
    - d. Studies: Currently, most studies are limited to in vitro evaluations, which showed high levels of accuracy and decreased time to pathogen and resistance mechanism identification. Limited clinical evidence; however, two small single-center studies have evaluated the use of Nanosphere technology to augment clinical decisions. These studies showed a decrease in time to appropriate antibiotic, in addition to decreased LOS and overall cost.
11. Chromogenic media
    - a. Mechanism
        - i. Microbiological media used to identify different microorganisms by color production
        - ii. Growth media use enzyme substrates that release colored dyes on hydrolysis, with a wide range of enzymes that can be targeted
        - iii. Potential advantage of being able to detect polymicrobial growth
    - b. Sensitivity and specificity: 95%–100%
    - c. Limitations
        - i. Many different companies make different chromogenic agar media (Brilliance, chromID, CHROMagar). Slight differences in sensitivity and specificity were seen in studies; however, all were within acceptable ranges.
        - ii. Time to identification is longer than with other rapid diagnostic tests.
        - iii. Different manufacturers' chromogenic agar produces different colors for positive identification. Readers of chromogenic agar should be sufficiently trained and familiar with the product used by the local institution.
    - d. Application
        - i. Isolation of *S. aureus* from other *Staphylococcus* spp.
        - ii. Detection of methicillin resistance among *S. aureus*
        - iii. Detection of vancomycin resistance
        - iv. Detection of specific Enterobacterales: *Salmonella, E. coli* O157, extended-spectrum β-lactamase (ESBL) production
        - v. Differentiation of different *Candida* spp.
        - vi. Detection of KPC
    - e. Studies: Many clinical studies have shown significant advantages over conventional culture media. With the advent of newer technology and shorter detection times, the clinical applicability of chromogenic media may be limited. However, few microbiology laboratories have implemented rapid diagnostic methods because of the considerable upfront costs. Centers where chromogenic media are being used may continue to rely on this technology.

Table 5. Examples of Rapid Diagnostic Tests of Positive Blood Cultures and Their Characteristics

Assay Technology	Manufacturer/ Trade Name	Organisms/Antimicrobial Resistance Targets	Detection Time After Positive Growth on Blood Culture
PNA FISH	• AdvanDx/PNA FISH, Traffic Light • AdvanDx/ QuickFISH	*S. aureus*, CoNS, *E. faecalis*, *E. faecium*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*	1.5 hr – PNA FISH 20 min – QuickFISH – Not currently FDA approved for *Candida* spp.
PCR	• BD GeneOhm/ Staph SR • Cepheid/Xpert MRSA	*S. aureus*, CoNS/*mecA* (methicillin)	1–2 hr
PCR	• BioFire/ FilmArray	*Enterococcus* spp., *L. monocytogenes* *S. aureus*, *S. agalactiae*, *S. pneumoniae*, *S. pyogenes*/*mecA* (methicillin), vanA/B (vancomycin) *A. baumannii*, *H. influenzae*, *N. meningitidis*, *P. aeruginosa*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *Proteus* spp., *S. marcescens*/KPC (carbapenem) *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*	1 hr – Direct from blood culture media
MALDI-TOF	• BioMérieux/ Vitek MS • Bruker/ Microflex	Several pathogens, including bacteria, yeast, mold, mycobacteria/resistance mechanisms are in development	10–30 min
Nanoparticles (Microarray)	• Nanosphere/ Verigene	*S. aureus*, *S. epidermidis*, *S. lugdunensis*, *S. anginosus*, *S. agalactiae*, *S. pneumoniae*, *S. pyogenes*, *E. faecalis*, *E. faecium*, *Staphylococcus* spp., *Streptococcus* spp., *Micrococcus* spp., *Listeria* spp./*mecA* (methicillin), vanA (vancomycin), vanB (vancomycin) *E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. aeruginosa*, *S. marcescens*, *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Proteus* spp./ CTX-M (ESBL), IMP (carbapenemase), KPC (carbapenemase), NDM (carbapenemase), OXA (carbapenemase), VIM (carbapenemase) *Candida* spp. in development	2 hr – Direct from blood culture media

Table 5. Examples of Rapid Diagnostic Tests of Positive Blood Cultures and Their Characteristics[a] *(continued)*

Assay Technology	Manufacturer/ Trade Name	Organisms/Antimicrobial Resistance Targets	Detection Time After Positive Growth on Blood Culture
Chromogenic media	- CHROMagar	*S. aureus*, MRSA, *Enterococcus* spp.,VRE, *S. agalactiae, E. coli* (Shiga toxin, EC-O157), *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *Acinetobacter* spp., *Yersinia* spp.; KPC (carbapenem), CTX-M (ESBL) *C. albicans*, *C. tropicalis*, *C. krusei*	24–48 hr

ESBL = extended-spectrum β-lactamase; KPC = *Klebsiella pneumoniae* carbapenemase; MALDI-TOF = matrix-assisted laser desorption-ionization/time of flight; MRSA = methicillin-resistant *S. aureus*; NDM = New Delhi metallo-β-lactamase; PCR = polymerase chain reaction; PNA FISH = peptide nucleic acid fluorescence in situ hybridization; VRE = vancomycin-resistant enterococci.

Reproduced with permission from: Goff DA, Jankowski C, Tenover F. Using rapid diagnostic tests to optimize antimicrobial selection in antimicrobial stewardship programs. Pharmacotherapy 2012;32:677-87.

Table 6. Reasonable Empiric Treatment Approach Associated with Detection of Antimicrobial Resistance Encoding Genes from Rapid Diagnostic Tests for Positive Blood Cultures[a]

Resistance Genes	Species	Recommended Therapy	Alternative Therapy
mecA-negative	*S. aureus*	Oxacillin Nafcillin Cefazolin	Vancomycin (if intolerance to β-lactams)
mecA-positive	*S. aureus*	Vancomycin	Daptomycin Linezolid Ceftaroline
vanA/B-negative	*E. faecalis*	Ampicillin	Vancomycin (if allergic to β-lactams)
vanA/B-positive	*E. faecalis*	Daptomycin	Linezolid
vanA/B-negative	*E. faecium*	Vancomycin	Daptomycin (if intolerance to vancomycin)
vanA/B-positive	*E. faecium*	Daptomycin	Linezolid
CTX-M (ESBL)[a]	Enteric gram-negative pathogens	Carbapenems (ertapenem, imipenem, meropenem)	Ceftazidime/avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam Cefiderocol
KPC[a]	*K. pneumoniae* and other enteric gram-negative pathogens	Ceftazidime/avibactam Meropenem/vaborbactam Imipenem/cilastatin/ relebactam	Colistin/polymyxin B Tigecycline/eravacycline Cefiderocol
NDM carbapenemase[a]	*K. pneumoniae* and other enteric gram-negative pathogens	Cefiderocol Aztreonam + ceftazidime/ avibactam	Colistin/polymyxin B Tigecycline
VIM or IMP carbapenemase[a]	*P. aeruginosa*	Colistin/polymyxin B Aztreonam Cefiderocol	

Table 6. Reasonable Empiric Treatment Approach Associated with Detection of Antimicrobial Resistance Encoding Genes from Rapid Diagnostic Tests for Positive Blood Cultures[a] *(continued)*

Resistance Genes	Species	Recommended Therapy	Alternative Therapy
OXA β-lactamase[a]	*P. aeruginosa* and Enterobacterales	Colistin/polymyxin B Carbapenem[b] Ceftazidime-avibactam[c]	Cefiderocol
OXA β-lactamase[a]	*A. baumannii*	Minocycline + high-dose ampicillin-sulbactam Sulbactam/durlobactam + a carbapenem	Cefiderocol Colistin/polymyxin B Tigecycline Eravacycline Carbapenem[b]

[a] Resistance mechanisms associated with gram-negative pathogens are more complicated. Often, there is more than one resistance mechanism. Hence, the recommended therapies represent reasonable empiric approaches before full antimicrobial susceptibility reports. However, therapy may be tailored to either a broader or a narrower spectrum (*Clin Infect Dis*. 2024 Aug 7:ciae403).

[b] Carbapenem may have a higher MIC in the presence of OXA β-lactamase. If using carbapenem, may consider using maximal doses.

[c] Not active against metallo-β-lactamases.

Patient Case

3. A 54-year-old man is admitted to the medical ICU with acute necrotizing pancreatitis. He is found to have an infected pancreatic abscess, which is being treated with meropenem and vancomycin. One week into the course, the patient develops a fever and leukocytosis. He also becomes hemodynamically unstable and oliguric. He is initiated on caspofungin empirically to cover for possible invasive candidiasis. Blood cultures are obtained, which become positive with a preliminary result of yeast. This institution is equipped with PNA FISH technology, which identifies the yeast as *Candida parapsilosis* on day 2 of therapy. The patient remains hemodynamically unstable. Which is the most appropriate choice for this patient's antifungal therapy?
   A. Continue caspofungin while fungal susceptibilities are finalized.
   B. Change to voriconazole 6 mg/kg every 12 hours.
   C. Change to liposomal amphotericin 5 mg/kg/day.
   D. Change to fluconazole 400 mg intravenously daily.

C. Early *C. difficile* Identification: Nucleic acid amplification methods (PCR and loop-mediated isothermal amplification)
   1. Assays are targeting DNA sequence for the toxin A or toxin B gene.
   2. Turnaround time: 1–3 hours
   3. Sensitivity and specificity: 90%–96%
      a. Because of increased sensitivity, the false-positive rates may be increased.
      b. As the prevalence of *C. difficile* decreases, the positive predictive value decreases, which may lead to unnecessary overtreatment.
      c. Educational efforts should be made to discourage the practice of over-ordering *C. difficile* rapid nucleic acid amplification tests. In addition, clinicians should be discouraged from ordering serial tests, which was a common practice when enzyme immunoassays were used. Because the sensitivity is sufficiently high, serial ordering only furthers the chance of false positivity.

D. Early Identification of Fungal Organisms
  1. Up to 50% of patients with histopathologically proven invasive candidiasis have negative blood cultures.
  2. Cultures for *Aspergillus* lack sensitivity and may require significant growth time.
  3. Biopsies are often not feasible in critically ill patients.
  4. Surrogate markers of fungal infections are needed for early diagnosis and to avoid delays in treatment, which have been associated with worsened outcomes.
  5. β-d-Glucan
    a. Found in the cell membrane of most fungal pathogens (except for *Mucor* and *Cryptococcus*). Potentially a screening tool for *Candida*, *Aspergillus*, and *Pneumocystis*.
    b. Fungitell assay can detect β-d-glucan in serum and provide results within 2 hours.
    c. Variable cutoffs are described in the literature for a positive result. A suggested cutoff for positive results, as used in a recent study evaluating prophylactic and preemptive antifungal therapy in critically ill patients, is greater than 80 pg/mL.
    d. Considerable differences in sensitivity and specificity values have been seen in different populations.
    e. Consistently high negative predictive values and low positive predictive values have been seen for the diagnosis of invasive fungal infections, which suggests that it is best used as a screening-out tool when the values are low. Low positive predictive value may occur because many clinical scenarios could lead to false-positive results.
      i. Exposure to β-d-glucan–containing surgical supplies and topical products
      ii. Colonization with *Candida*
      iii. Thrush and mucositis
      iv. Cellulose membranes from dialysis filters
      v. Bacterial infections
      vi. Receipt of β-lactam antibiotics, albumin, or immunoglobulins
    f. When used as a tool to potentially initiate treatment, optimal results occur when two consecutive tests are positive.
    g. Nonspecific fungal element makes interpretation difficult. May detect elements from *Aspergillus*, *Candida*, and *Pneumocystis*. Does not detect different species.
    h. Has been evaluated in combination with clinical prediction scores for invasive candidiasis in critically ill patients for initiating empiric antifungal therapy. When using β-d-glucan as a screening tool, empiric echinocandin therapy does not result in any significant differences in clinical outcomes compared with placebo.
    i. A recent multicenter, randomized controlled trial found no difference in 28-day mortality when antifungal treatment was guided by β-D-glucan compared with control where initiation of antifungals was culture-driven (*Intensive Care Med*. 2022;48(7):865-875).
  6. T2 magnetic resonance
    a. Nanodiagnostic approach, which detects amplified *Candida* DNA. Similar to traditional MRI techniques, but done on a micro scale.
    b. Performed on whole blood, where magnetic particles that are coated with agents specific for binding to *Candida* DNA.
    c. When *Candida* is present in whole blood, it will bind to the particles and cluster, causing microscopic disruptions in the magnetic fields.
    d. Currently, FDA approved for 5 pathogenic *Candida* species *(C. albicans, C. glabrata, C. parapsillosis, C. tropicalis, C. kruseii)*
    e. High sensitivity (91%) and specificity (98%) but lacks clinical study application
  7. Mannan/Anti-mannan
    a. Mannan is a polysaccharide component of the fungal cell wall that is specific to *Candida* spp.
    b. A commercially available latex agglutination and enzyme immunoassay exists for both mannan antigen and anti-mannan antibibodies that develop in response to mannan.

   c. Both tests are more specific than the β-d-glucan test, but they are not as sensitive.
   d. A meta-analysis that included studies in non-neutropenic critically ill patients found improved sensitivity and specificity of both tests when used in combination. It also demonstrated a varied sensitivity depending on the *Candida* spp (C. albicans with the highest and *C. parapsilosis* with the lowest).
8. Galactomannan
   a. Cell wall component of *Aspergillus* spp.
   b. Platelia enzyme immunoassay can detect galactomannan in serum or other sterile fluids (bronchoalveolar lavage) within 4 hours.
   c. Variable sensitivity and specificity, with generally better positive and negative predictive values for the detection of *Aspergillus* in the patient population with hematologic malignancies than in the solid organ transplant (SOT) population
   d. False positives can occur with the simultaneous administration of certain β-lactam antibiotics (piperacillin/tazobactam, amoxicillin/clavulanic acid) or the presence of other invasive mycoses (*Penicillium*, histoplasmosis, blastomycosis).
9. PCR
   a. An FDA-approved assay is available for detecting *Candida* spp. only.
   b. This test allows for the early detection of candidemia.
   c. This assay has high sensitivity and specificity and a good negative and positive predictive value.
   d. Colonization may decrease specificity and using the test too early (e.g., prior to onset of new symptoms) may decrease sensitivity.

E. Procalcitonin (PCT)
   1. An inflammatory biomarker that reflects host response to bacterial infections
   2. PCT synthesis is up-regulated by bacterial toxins and certain bacterial proinflammatory mediators such as interleukin (IL)-1b, IL-6, and tumor necrosis factor alpha (TNFα), but it is neutral to cytokines that are normally released for viral infections such as interferon-γ. Usual concentrations of PCT are undetectable (less than 0.05 mcg/L). However, on exposure to bacterial toxins, PCT is rapidly released within 2–4 hours. The plasma half-life of PCT is 24 hours. Concentrations in the literature for infected patients vary greatly; however, it appears that a higher max concentration of PCT during infection correlates with a higher incidence of mortality.
   3. PCT is used in many roles, including the diagnosis and prognostication for sepsis. IDSA stewardship guidelines recommend serial measurements be used in conjunction with other stewardship interventions to decrease antibiotic use. The Surviving Sepsis Campaign provides a weak recommendation (weak recommendation, low quality of evidence) for the use of PCT to assist clinicians in the discontinuation of empiric antibiotics when no evidence of infection is found among patients with sepsis.
   4. For clinical decisions regarding antibiotic use and duration, PCT has been evaluated for antibiotic initiation, antibiotic cessation, and the combination of both strategies. These strategies assume PCT availability from an institutional laboratory. If the PCT turnaround time is more than 24 hours, the effects of minimizing antimicrobial treatment days may be limited.
   5. It is unclear how to interpret PCT levels in certain patient populations; however, PCT use is not precluded in these populations as long as providers are aware of limitations. According to current evidence, PCT should be used with caution in the following patient populations:
      a. Chronic kidney disease: Patients with chronic kidney disease have higher baseline levels of PCT.
      b. PCT levels can be elevated among patients during times of noninfectious conditions such as trauma, surgery, burns, immunomodulator therapy that increases proinflammatory cytokines, cardiogenic shock, during peritoneal dialysis, and cirrhosis.

6. According to current evidence, PCT should not routinely be measured in patients without signs and symptoms of infection. The decision to initiate patients on antibiotics without signs and symptoms of infection using PCT alone would probably lead to antimicrobial overuse and possible adverse effects associated with antimicrobial therapy. In a PCT study of critically ill patients, 1200 patients were randomized to either a PCT alert strategy or a standard of care. For those randomized to intervention, a PCT concentration greater than 1.0 mcg/L generated an alert that mandated clinical intervention, which included microbiological cultures, additional radiologic assessment, and/or initiation or expansion of antimicrobial coverage. Overall, this strategy did not lead to an improvement in mortality or time to appropriate antibiotics. In contrast, patients experienced a greater need for mechanical ventilation, prolonged ICU LOS, and prolonged antibiotic use.
7. In critically ill patients with signs and symptoms of infection, a baseline PCT (at the time of the symptoms) should not be used to determine whether antibiotics should be initiated. The compliance rate for withholding antibiotics for a low PCT in this scenario has consistently been low. The compliance rate in clinical practice is likely even lower than that in clinical studies; however, this has not been evaluated. If a baseline PCT is obtained, it should be used to trend the PCT for the possible early discontinuation of antibiotics. In a study of patients with signs and symptoms of infection to determine whether a PCT-guided strategy would limit the initiation of antibiotics, no difference in antibiotic use was seen. However, this was probably because only 36% of clinicians were compliant with the recommendation to withhold antimicrobials when the PCT was low. This is in stark contrast with the 86% compliance rate with the recommendation to initiate antibiotics when the PCT was high.
8. Critically ill patients with signs and symptoms of infection should have a baseline PCT obtained for trending purposes. A low PCT (or substantial decrease from baseline) during antibiotic treatment should be used to shorten the duration of antimicrobial therapy. This could be accomplished through either eliminating unnecessary antibiotics in patients who are not infected or shortening the course of therapy for patients who are infected. This strategy has been proven safe and effective in a wide spectrum of critically ill patients. Several studies have evaluated the utility of a PCT-guided strategy for determining the appropriate time to discontinue and/or de-escalate antibiotics. These studies consistently show that PCT guidance for discontinuing antimicrobial therapy led to decreases in antibiotic use without an untoward outcome effect. This has been shown in various ICU populations, in patients with different severity of illness, and in those with proven infections. The largest PCT study of critically ill patients (n=1575) was published in 2016. It demonstrated a significant decrease in the use of antimicrobials (median 5 days vs. 7 days) and 28-day mortality (20% vs. 25%; p=0.012). A recent meta-analysis showed that use of PCT to guide discontinuation of antimicrobial therapy may have a short-term mortality benefit.
9. A recent prospective study showed that the inability to decrease PCT by at least 80% by day 4 was an independent predictor of mortality.
10. Many different PCT guidance algorithms exist; Figure 2 represents a reasonable approach to using PCT for antibiotic cessation. In certain scenarios, PCT concentrations may be affected. For example, some clinicians recommend using different cutoffs (e.g., greater than 0.5 mcg/L) in patients with stage 5 chronic kidney disease or requiring dialysis. Furthermore, in some studies, the PCT cutoff is greater than 1.0 mcg/L among patients with recent surgery.
11. PCT levels have been elevated in patients with COVID-19, although interpretation is challenging as this could represent bacterial co-infection, could be a marker of severity of acute respiratory distress syndrome, or respiratory failure could cause immune dysregulation that increases the production of cytokines. Due to the unclear cause of elevated PCT in COVID-19, it is not advisable to use the PCT level by itself to guide antibiotic therapy.

F. MeMed BV
   1. A host response diagnostic that differentiates bacterial from viral infection at the point of need by computationally integrating the levels of three host immune response proteins (tumor necrosis factor-related, apoptosis-inducing ligand [TRAIL], interferon gamma inducible protein-10 [IP-10], and C-reactive protein [CRP]) into a score indicating the likelihood of a bacterial immune response or co-infection versus a viral infection.
      a. Score: 0–34 = viral infection, 35–65 = equivocal, 66–100 = bacterial infection
      b. Delivers results in 15 minutes
   2. Additional data is needed before wide spread clinical implementation

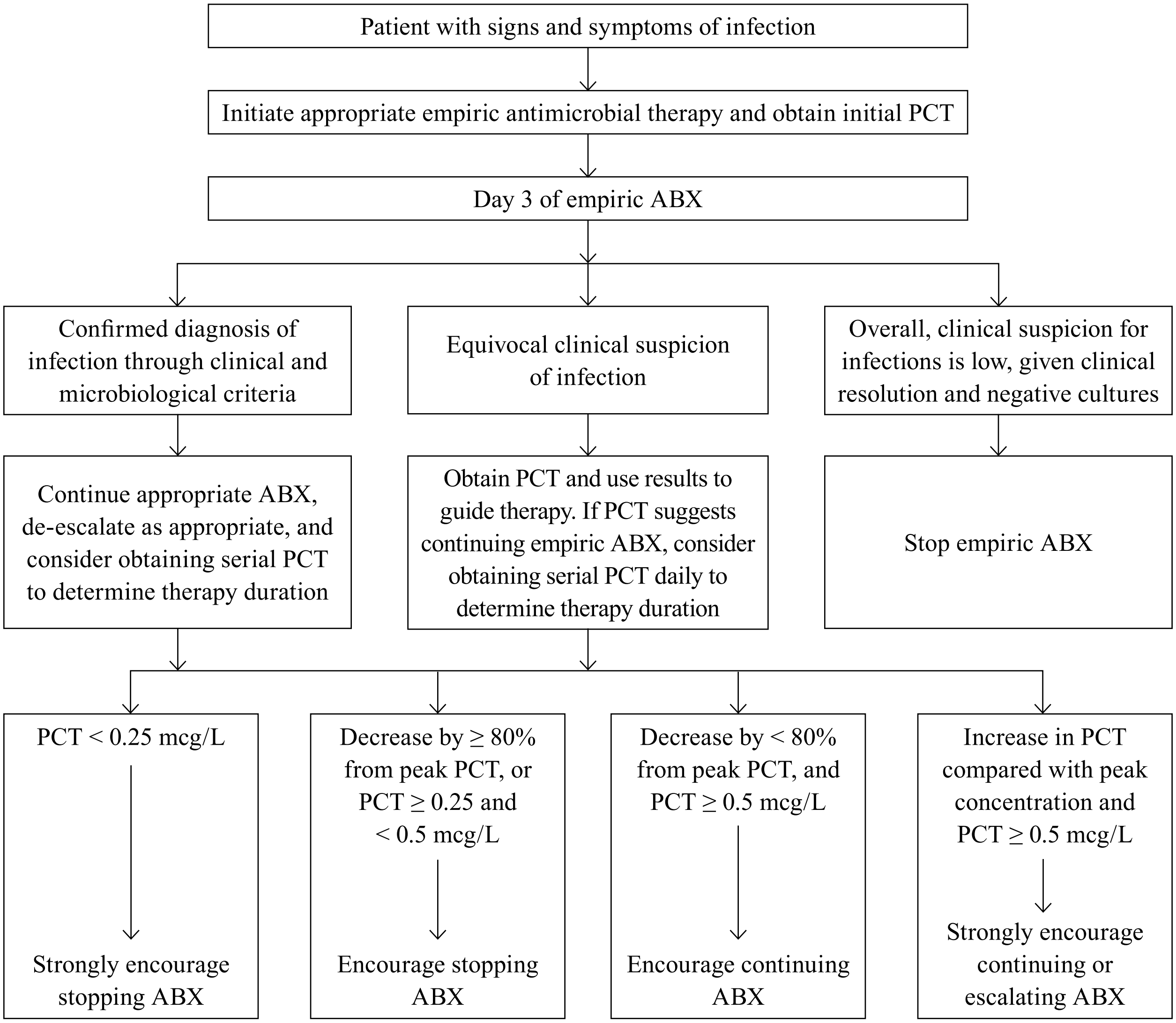
Patient with signs and symptoms of infection
Initiate appropriate empiric antimicrobial therapy and obtain initial PCT
Day 3 of empiric ABX
Confirmed diagnosis of infection through clinical and microbiological criteria
Equivocal clinical suspicion of infection
Overall, clinical suspicion for infections is low, given clinical resolution and negative cultures
Continue appropriate ABX, de-escalate as appropriate, and consider obtaining serial PCT to determine therapy duration
Obtain PCT and use results to guide therapy. If PCT suggests continuing empiric ABX, consider obtaining serial PCT daily to determine therapy duration
Stop empiric ABX
PCT < 0.25 mcg/L
Strongly encourage stopping ABX
Decrease by ≥ 80% from peak PCT, or PCT ≥ 0.25 and < 0.5 mcg/L
Encourage stopping ABX
Decrease by < 80% from peak PCT, and PCT ≥ 0.5 mcg/L
Encourage continuing ABX
Increase in PCT compared with peak concentration and PCT ≥ 0.5 mcg/L
Strongly encourage continuing or escalating ABX

Figure 2. Sample procalcitonin-guided antimicrobial management algorithm.

ABX = antibiotics; PCT = procalcitonin.

Patient Case

4. A 64-year-old woman is admitted to the medical ICU with possible community-acquired pneumonia. The patient is initiated on ceftriaxone and azithromycin. Chest radiography reveals focal infiltrate. On admission, she is dyspneic with a respiratory rate of 33 breaths/minute. Her vital signs and laboratory values are as follows: blood pressure 90/50 mm Hg, heart rate 101 beats/minute, WBC 18 x 10^3 cells/mm^3, and lactate 4.2 mmol/L. A PCT is obtained on admission. The results are available 12 hours after antibiotics are initiated. The PCT result is 0.1 mcg/L. Which is the most appropriate option, given the PCT result?
   A. Continue all current antibiotics.
   B. Discontinue all antibiotics.
   C. Escalate antibiotics to piperacillin/tazobactam.
   D. Discontinue ceftriaxone only.

V. INTERPRETING SUSCEPTIBILITY REPORTS

A. Rationale: Identifying microorganisms and antibiotic susceptibilities is integral to the care of critically ill patients with infections. An understanding of the microbiology laboratory methods for pathogen identification and susceptibility testing will further equip critical care pharmacists with the ability to use the most appropriate antimicrobial regimens for the treatment of critical care–associated infections. Standards for antimicrobial identification, sensitivity testing, and determination of MIC breakpoints are determined by the Clinical & Laboratory Standards Institute (CLSI). CLSI is a volunteer-driven standards development organization that promotes the development and use of laboratory consensus standards and guidelines within the healthcare community.

B. Methods for Antimicrobial Susceptibility Testing (AST)
   1. Disk diffusion (Kirby-Bauer)
      a. Test agar plates are swabbed with a standardized concentration of the test organisms; paper disks containing a defined antibiotic concentration are then placed on the plates. The diameter of the zone of inhibited growth is inversely proportional to the MIC value.
      b. Usually reported qualitatively as sensitive, intermediate, or resistant
   2. Dilution methods (i.e., broth dilution, agar dilution)
      a. Two-fold serial dilutions of antibiotics are prepared (in either broth or agar), which are then inoculated with a standardized concentration of test organisms.
      b. The MIC is determined.
      c. Precision of this method is within one 2-fold concentration in either direction.
      d. Many prefabricated broth microdilution plates are commercially available.
   3. E-test
      a. A calibrated plastic strip with a range of continuous MIC values (with fifteen 2-fold dilutions) is placed on an inoculated agar plate. The MIC can be determined by the intersection between the zone of inhibition and the edge of the calibrated strip.
      b. Complement other systems to determine the MIC for specific antibiotics and test for resistance and for confirmatory testing
      c. Studies have shown that the reading of the exact MIC on an E-test strip is subject to the user's interpretation and could lead to a one- or two-dilution error in either direction compared with standardized methods.

4. Automated systems (e.g., Vitek, Microscan, Sensititre, Phoenix, Accelerate Pheno test)
    a. Uses computerized algorithms for interpreting MIC values
    b. Can usually perform AST more quickly than traditional methods
    c. More than 80% of all clinical microbiology laboratories report using an automated system as their primary method of susceptibility testing.
    d. May be unable to detect certain resistance mechanisms (i.e., inducible enzymes)
    e. Standard inoculums of pathogens are used. For infections in which the in vivo inoculum may be higher, certain antimicrobials may have higher MIC values.
5. Specific confirmatory tests for antimicrobial resistance
    a. Macrolide-lincosamide-streptogramin resistance
        i. Strains of *Staphylococcus* spp. can have a transferable resistance mechanism called macrolide-lincosamide-streptogramin, which is inducible by clindamycin and can lead to treatment failure.
        ii. Inducible resistance is not detected by routine AST.
        iii. Detected using double-disk diffusion
    b. ESBL
        i. CLSI procedures exist for *K. pneumoniae*, *Klebsiella oxytoca*, *E. coli*, and *Proteus mirabilis*.
        ii. Initial screening with susceptibility testing for ceftazidime, aztreonam, cefotaxime, or ceftriaxone
        iii. Confirmatory testing with broth microdilution, disk diffusion, or E-test strips. Presence of ESBL is confirmed if adding clavulanic acid results in three 2-fold dilution decreases in the paired-cephalosporin MIC.
        iv. Beginning in 2010, CLSI adopted lower MIC breakpoints for many cephalosporins for Enterobacterales (see Table 7). The rationale for this change is that the lower MIC may more readily detect the presence of ESBL, hence eliminating the need for the labor-intensive confirmatory tests. Compliance with this new practice is variable among clinical microbiology laboratories. Clinicians should inquire within their local clinical microbiology laboratory regarding whether the new standards have been adopted. If a microbiology laboratory has adopted the new CLSI recommendations for ESBL detection, confirmatory tests are unnecessary.

Table 7. Changes to CLSI Enterobacterales Breakpoints with 2023 Updates

Agent	Pre-2010 CLSI Breakpoints			2023 CLSI Breakpoints		
	S	**I**	**R**	**S**	**I**	**R**
Cefazolin[a]	≤ 8	16	≥ 32	≤ 2	4	≥ 8
Cefazolin[b]	≤ 8	16	≥ 32	≤ 16	—	≥ 32
Cefotaxime	≤ 8	16–32	≥ 64	≤ 1	2	≥ 4
Ceftriaxone	≤ 8	16–32	≥ 64	≤ 1	2	≥ 4
Ceftazidime	≤ 8	16	≥ 32	≤ 4	8	≥ 16
Aztreonam	≤ 8	16	≥ 32	≤ 4	8	≥ 16

[a] Cefazolin used as therapy for infections other than uncomplicated UTIs.

[b] Cefazolin used as therapy for uncomplicated UTIs.

CLSI = Clinical & Laboratory Standards Institute; UTI = urinary tract infection.

    c. AmpC β-Lactamase
        i. Inhibitor-resistant β-lactamase (e.g., clavulanic acid, tazobactam, avibactam, vaborbactam, durlobactam, and relebactam)

   - ii. Maintains sensitivity with cephamycins (e.g., cefotetan, cefoxitin) and cloxacillin
   - iii. Confirmatory test with E-test containing cephamycin alone or a combination of cephamycin and cloxacillin. If the MIC is decreased by more than three 2-fold dilutions, the presence of AmpC β-lactamase is confirmed.
- d. Carbapenemase
   - i. Metallo-β-lactamase (e.g., New Delhi metallo-β-lactamase [NDM]; Verona integrin-encoded metallo-β-lactamase [VIM]); imipenimase-type carbapenemase)
      - (a) Hydrolyzes both β-lactam and carbapenem antibiotics, but aztreonam maintains susceptibility. Clinically, about 80% of metallo-β-lactamase–containing pathogens are resistant to aztreonam because of other resistance mechanisms.
      - (b) Zinc-mediated metallo-β-lactamase can be repressed by ethylene-diamine tetraacetic acid (EDTA). Reduction in imipenem MIC by more than three 2-fold dilutions in the presence of EDTA confirms presence of zinc-mediated metallo-β-lactamase.
   - ii. KPC
      - (a) KPC enzyme can produce a slightly higher MIC that may still be in the range considered sensitive. This is in contrast to other carbapenem-resistant mechanisms in *Pseudomonas* and *Acinetobacter*, which generally produce a fully resistant MIC. Hence, a carbapenem MIC of 1 mcg/mL or greater in an Enterobacterales should be evaluated through further confirmatory testing.
      - (b) Modified Hodge test should be performed for pathogens with an elevated carbapenem MIC.
         - (1) Place standard sensitive *E. coli* strain on entire plate.
         - (2) Place meropenem or carbapenem disk in center of test area.
         - (3) Streak test organism in a straight line from edge of carbapenem disk to edge of plate (up to four different organisms can be tested).
         - (4) Positive carbapenemase results from modified Hodge test have a clover leaf–like indentation of the *E. coli* growing along the test organism's streak.
      - (c) Starting in 2010, CLSI lowered the susceptibility breakpoints for carbapenem (0.5 mcg/mL and 1.0 mcg/mL or less for ertapenem and other carbapenems, respectively), with the intent of eliminating the need for confirmatory tests.
         - (1) Clinicians should inquire about the practices of their local microbiology laboratory regarding carbapenem susceptibility.
         - (2) Particularly when confirmatory tests are not being performed, and a laboratory continues to use the older MIC breakpoints, a higher clinical suspicion for carbapenemase is warranted.
         - (3) Ertapenem resistance seen on AST is a sensitive marker for the presence of carbapenemase. Before the 2010 reclassification of carbapenem susceptibility breakpoints, there were reports of up to 46% of clinical isolates with genotypic evidence of KPC-producing enzymes being inadvertently labeled as imipenem sensitive.
         - (4) Deleterious outcomes associated with the use of carbapenems in carbapenemase-producing organisms have been reported.

C. MIC Breakpoints: Determining the correct MIC breakpoint by the governing standards is a complicated process. CLSI promotes the development of voluntary consensus standards within the medical community. Determining CLSI breakpoints could be based on several conflicting interests, which may include some of the following:

1. Microbiological: MIC that distinguishes wild-type bacteria from those that have acquired additional resistance mechanisms

2. PK/PD: Derived from human or animal data and modeled to determine the likelihood that standard prescribed doses will meet specified PD criteria for suppressing bacterial growth
3. Breakpoints that may decrease the need for confirmatory tests, hence decreasing the microbiology laboratory workload. Such an approach, although possibly sensitive for determining the presence of resistance mechanisms, may potentially lead to the compensatory use of broader antimicrobials.
4. The CLSI breakpoints may be inconsistent with the breakpoints established by the FDA. Automated systems report MIC breakpoints according to FDA approvals. Changes to reporting and labeling require additional clearance from the FDA. Unfortunately, the FDA labeling may not be up to date with the current CLSI recommendations. Hence, despite newer CLSI recommendations, many institutions may still be reporting susceptibility results that are based on their respective FDA labeling breakpoints. These breakpoints may result in pathogens being labeled as sensitive, even though, according to the current CLSI standards, they would be considered resistant.
5. The exact MIC breakpoints that are used by a local microbiology laboratory can be variable, depending on the laboratory's adaptation of new standards. In addition, there are significant variations in the FDA-approved breakpoints used by automated AST methods and updated CLSI guidelines. Once again, this highlights the importance of a clinician's understanding of the exact methods and breakpoints that are used in his or her institution.

D. Minimum recommended information that critical care pharmacists should recognize about their local microbiology laboratory practices
   1. Routine methods for AST
   2. Availability of rapid diagnostic tests for speciation or resistance gene identification
   3. If additional tests are available (E-test, genotyping, etc.) and how to go about requesting additional information
   4. Are confirmatory tests for resistance mechanisms routinely done (e.g., double-disk diffusion for macrolide-lincosamide-streptogramin–inducible resistance, ESBL and KPC confirmatory tests)?
   5. What is the usual procedure for censoring the AST results?
      a. Does the AST result try to guide clinical decision (i.e., if pathogen were sensitive to oxacillin, would vancomycin results be censored)?
      b. If certain resistance mechanisms are detected, would the laboratory automatically update susceptibility results (i.e., if ESBL were detected, would β-lactam/β-lactamase combination antibiotics automatically be changed to resistant)?
      c. Are any antibiotics part of the standard panel but routinely hidden from clinical reports?
      d. Most microbiology laboratories would retain all the information, even if parts of the results had been censored. Critical care pharmacists should consider contacting the microbiology laboratories to see whether additional information regarding the pathogen is available.
   6. When an MIC is reported, is only the MIC breakpoint reported (i.e., MIC 2 mcg/mL or less), or is the actual MIC reported (i.e., 0.25 mcg/mL)?
   7. Are the breakpoints reported consistent with the updated CLSI recommendations?

E. Clinical Application of Interpreting AST
   1. The ideal application of AST interpretation and clinical therapeutics may include the following:
      a. Knowledge of the individual pathogen and the corresponding MIC breakpoints for each of the tested antibiotics
      b. Potential reasoning behind each of the clinical breakpoint designations (i.e., wild-type selection, PK/PD breakpoints assessment, screening for resistance)
      c. Accurate comprehension of the local AST methods used and potential limitations of the MIC reported

   d. Understanding of the tested antimicrobial's PD parameters, which conveys the highest likelihood for eradication of the microorganism
   e. Selecting the most appropriate antibiotic according to an assessment of the following:
      i. What genotypic resistance mechanisms may be suggested by the phenotypic representation of the AST?
      ii. How may the underlying resistance mechanisms affect the choice of antimicrobial therapy?
      iii. The PK characteristics of the medication and patient characteristics that may affect the antimicrobial's PK
      iv. The likelihood that the considered antimicrobial agent will reach its PD targets for optimal therapy at the local site of infection
      v. Selecting the antimicrobial according to a balance of antimicrobial stewardship principles, adverse effects profile, allergies, and cost
2. When an antimicrobial must be chosen despite its having a higher-than-ideal MIC, the penetration into the site of infection is questionable, or the correlation of PK and PD target attainment is not available, additional interventions may be required. Optimization of therapy should be tried through one or more of the following: using a higher dose, using administration strategies that may optimize PK/PD (i.e., extended- or continuous-infusion β-lactams), or combination therapy.

VI. MECHANISMS OF ANTIBACTERIAL RESISTANCE AND TREATMENT OF MULTIDRUG-RESISTANT PATHOGENS

A. Epidemiology and Clinical Significance: The WHO has identified antimicrobial resistance as one of the three greatest threats to human health.
   1. The NHSN for the CDC reports recent resistance rates among commonly encountered pathogens. More than 3000 U.S. hospitals participate in this national surveillance program, with as many as 100,000–300,000 pathogens reported and about 70% of the reporting from critical care sites. See Table 8 for selected resistance rates in different hospital-acquired infections.
   2. Resistance rates continue to be high, with trends toward an increase in certain pathogens compared with the reports from previous years.
      a. The CDC reports on antimicrobial-resistant threats and classifies them as urgent or serious.
         i. An urgent antimicrobial-resistant threat indicates a situation requiring immediate and aggressive action because of high mortality and limited treatment options. These threats include:
            (a) Carbapenem-resistant *Enterobacterales*
            (b) Carbapenem-resistant *Acinetobacter*
            (c) *Candida auris*
         ii. A serious antimicrobial-resistant threat signifies a need for prompt and sustained action to prevent further resistance development. These threats include:
            (a) MRSA
            (b) Vancomycin-resistant *Enterococcus*
            (c) ESBL-producing *Enterobacterales*
            (d) Multidrug-resistant *P aeruginosa*
   3. Resistant pathogens consistently correlate with worse clinical outcomes, which is partially explained by the higher likelihood of empiric treatment with a resistant antibiotic.

4. The antibiotic pipeline has slowed down considerably, with consistent decreases in FDA approvals of antimicrobial agents during the past 3 decades. The combination of prevailing resistance, including the emergence of pan-resistant pathogens, with the lack of new antimicrobial agents presents a potential global health problem.
5. An understanding of resistance mechanisms would assist the ICU clinician in effectively treating current resistant pathogens while incorporating antimicrobial stewardship principles to prevent further resistance. See Table 9 for common mechanisms of resistance.

Table 8. Recent Resistance Rates in Hospital-Acquired Infections 2018-2021

Pathogen	CLABSI % Resistance	CAUTI % Resistance	SSI % Resistance
Gram-negative Bacteria			
Multidrug-resistant[a] *P aeruginosa*	14.2	8.7	3.9
Gram-positive Bacteria			
S. aureus Oxacillin resistant	44.9	39.8	39.2
E. faecalis Vancomycin resistant	3.8	2.8	2.4

[a] Multidrug resistant is defined as being either intermediate or resistant to at least 1 drug in 3 of the following 5 classes: third- and fourth-generation cephalosporins, fluroquinolones, aminoglycosides, carbapenems, and piperacillin and/or piperacillin-tazobactam (definition according to the CDC National Healthcare Safety Network).

CAUTI = catheter-associated urinary tract infection; CLABSI = central–line associated bloodstream infection; SSI = surgical site infection.

Table 9. Common Resistance Mechanisms

Antibacterial Agent	Mechanism of Resistance
β-Lactams	β-Lactamases (AmpC, ESBL, KPC) Reduced permeability Altered penicillin binding proteins Increased efflux
Fluoroquinolones	Altered DNA gyrase and topoisomerase Increased efflux Decreased protein targets
Macrolides	Increased efflux Methylating enzymes
Aminoglycosides	Aminoglycoside-modifying enzymes Increased efflux Modification of target proteins
Glycopeptides	Altered target Decreased permeability
Tetracyclines	Increased efflux Protection of target proteins
Trimethoprim	Increased efflux Altered dihydrofolate reductase
Rifamycin	Altered RNA polymerase

B. Mechanisms of Resistance (bacteria often possess several mechanisms)
  1. Decreased permeability (i.e., porin loss, thickened cell wall)
  2. Increased efflux (i.e., macrolide efflux pump)
  3. Target modification (i.e., alteration in penicillin-binding proteins)
  4. Hydrolysis (i.e., β-lactamases, aminoglycoside-modifying enzymes)

C. Factors Associated with Resistance Acquisition
  1. Crowding of patients with high levels of disease acuity and/or antimicrobial use
  2. Prolonged hospital LOS
  3. Colonization pressure: Proportions of people colonized with resistant bacteria. Combated by strict compliance with infection control procedures to prevent colonization, adequate nurse staffing ratios, and hand hygiene
  4. Use of invasive devices (endotracheal tubes, intravascular catheters, and urinary catheters)
  5. Previous or prolonged use of antibiotics

D. Clinical Approach to Common Pathogen Resistance Seen in Critically Ill Patients (for further information, please see the IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections [*Clin Infect Dis*. 2024 Aug 7:ciae403. https://doi.org/10.1093/cid/ciae403])
  1. ESBL
    a. Confers resistance to third-generation cephalosporins and aztreonam
    b. Found primarily in *E. coli* and *K. pneumonia*e spp. but can also be seen in other Enterobacterales.
    c. Carbapenems should be considered the drug of choice in severe infections.
    d. Non–β-lactams could be used if they showed sensitivity on AST; however, because ESBLs are usually plasmid mediated, there are often other acquired resistance mechanisms. The rates of cross-resistance to other classes of antibiotics are 55%–100%.
    e. β-lactam/β-lactamase inhibitors and cefepime often have in vitro activity, though clinical failures have been reported.
      i. A previous post hoc analysis found that use of β-lactam/β-lactamase inhibitors was not associated with worse outcomes for ESBL-producing *E. coli* bacteremia compared with carbapenems.
      ii. However, a recent prospective randomized controlled noninferiority study evaluating definitive treatment of ceftriaxone-resistant *E. coli* or *K. pneumoniae* found increased mortality with piperacillin/tazobactam compared with meropenem (12.3% vs. 3.7%). These results do not support the use of piperacillin/tazobactam in the treatment of ESBL-producing organisms.
      iii. Data are conflicting regarding the use of cefepime for treating ESBL infections. Some studies show worse outcomes, whereas others show no difference compared with carbapenems. This may partly be explained by the cefepime MIC distribution. Traditionally (before 2014), the susceptibility breakpoint for cefepime for Enterobacterales was 8 mcg/mL or less. However, in 2014, CLSI recommended decreasing the sensitive cefepime MIC breakpoint to 2 mcg/mL. In addition, a new category for sensitive dose-dependent was created, where maximal doses of cefepime are recommended for MICs of 4 and 8 mcg/mL. Hence, for many years, cefepime may have been used in ESBL infections when the MIC was 4–8 mcg/mL, but doses were not optimized.
      iv. Of interest, a recent investigation correlated cefepime MIC to ESBL Enterobacterales with mortality, where a cefepime MIC of 1 mcg/mL or less was associated with significantly lower mortality compared with higher MIC values. Together, given the conflicting clinical results, it is difficult to endorse the use of cefepime for the treatment of ESBL infections. However, in a stable patient with an ESBL infection having a cefepime MIC of 1 mcg/mL or less, cefepime may be considered for consolidative therapy to minimize carbapenem use.

- f. Cefepime-enmetazobactam
    - i. FDA approved in 2024 for treatment of complicated UTIs including pyelonephritis caused by ESBL-producing gram-negative organisms, including organisms that produce CTX-M, SHV, TEM, and VEB
    - ii. Target bacteria include *E coli, K pneumoniae, P aeruginosa, P mirabilis*, and *E cloacae*.
    - iii. Does not have activity against KPC, metallo-β-lactamases, or some oxacillinases
    - iv. Cefepime-enmetazobactam, compared with piperacillin-tazobactam, met noninferiority as well as superiority for clinical cure and microbiologic eradication in patients with complicated UTIs or acute pyelonephritis.

2. AmpC β-lactamases
    - a. Confer resistance to penicillins and narrow-spectrum cephalosporins
    - b. β-Lactamase inhibitor resistant; hence, tazobactam and clavulanic acid would not provide additional coverage
    - c. Innate low-level production in many gram-negative bacteria (i.e., *Enterobacter*, *Citrobacter*, *Serratia*, *Morganella*, *Providencia*, and *Pseudomonas*). This low-level production leads to resistance against penicillin, ampicillin, and first-generation cephalosporins.
    - d. Genetic mutation leading to sustained high-level production is possible (derepressed mutants).
        - i. Theoretically, treatment with third-generation cephalosporins or broad-spectrum cephalosporins for non-derepressed mutants may select species with the mutation. The actual incidence of breakthrough infections is unknown with derepressed mutants when bacteria with innate AmpC β-lactamase production are treated with third-generation cephalosporins or extended-spectrum penicillins. However, it is believed to be low.
        - ii. Several epidemiologic studies have linked the use of third-generation cephalosporins with the increase in pathogenic species of AmpC hyperproducing Enterobacterales.
        - iii. Derepression confers resistance to third-generation cephalosporins and broad-spectrum penicillins (piperacillin, ticarcillin).
        - iv. Commonly occurs in *E. cloacae* and *Citrobacter freundii, Hafnia alvei, Klebsiella (Enterobacter) aerogenes, Yersinia enterocolitica*
        - v. Cefepime generally retains activity against derepressed mutants.
        - vi. Carbapenem and cefepime should be considered the drugs of choice in severe infections.
        - vii. Because derepression results from the mutation of a chromosomal-mediated β-lactamase, and not from transmitted plasmids, many pathogens with this mutation maintain sensitivity to other nonβ-lactam antimicrobials (e.g., fluoroquinolones, aminoglycosides).

Patient Case

5. A 74-year-old man is admitted to the surgical ICU after elective hip replacement surgery. The patient, who has a history of chronic pulmonary obstructive disease, cannot be weaned off the ventilator after surgery. During the patient's course, he develops signs and symptoms of infection. His vital signs and laboratory values are as follows: blood pressure 94/55 mm Hg, heart rate 114 beats/minute, temperature 101.9°F (38.8°C), WBC 18 x 10^3 cells/mm^3, and lactate 3.2 mmol/L. The patient is empirically initiated on piperacillin/tazobactam and vancomycin and given 2 L of crystalloid fluids; pan cultures are sent. Urinalysis reveals pyuria, positive leukocyte esterases, and nitrites. Blood and sputum cultures are negative, but urine culture shows *E. coli*. The patient's urinary catheter is removed, and vancomycin is discontinued. On day 3 of therapy, antibiotic susceptibility results are available. The patient's *E. coli* is resistant to third-generation cephalosporins with laboratory confirmation of the presence of ESBL. The laboratory reports the following antimicrobials and corresponding MIC values: piperacillin/tazobactam less than 2 mcg/mL – S; cefepime 4 mcg/mL – SDD; imipenem 0.5 mcg/mL – S; and ciprofloxacin 0.25 mcg/mL – S. The patient's vital signs and laboratory values are as follows: blood pressure 110/70 mm Hg, heart rate 98 beats/minute, respiratory rate 30 breaths/minute, temperature 98.7°F (37.1°C), and WBC 9 x 10^3 cells/mm^3. Which is the most appropriate antibiotic option?
   A. Change piperacillin/tazobactam to imipenem.
   B. Continue piperacillin/tazobactam alone.
   C. Change piperacillin/tazobactam to cefepime.
   D. Add ciprofloxacin to piperacillin/tazobactam.

3. Carbapenemase
   a. Seen in *Acinetobacter*, *Pseudomonas*, and Enterobacterales
   b. The global spread of carbapenem resistance has become an epidemic.
   c. The CDC continues to report that carbapenem-resistant Enterobacterales (CRE) is at an urgent hazard level, where high consequence and probability for widespread public health concerns exist.
   d. Confers resistance to most β-lactams, including carbapenems, cephalosporins, monobactam, and broad-spectrum penicillins
   e. Treatment options
      i. Tigecycline:
         (a) Glycylcycline antibiotic, which is structurally similar to tetracyclines
         (b) Mechanism of action: Inhibition of 30s ribosomal subunit
         (c) Spectrum of activity:
            (1) Gram-positive bacteria: *Enterococcus* (including vancomycin-resistant enterococci), *Listeria*, *Staphylococcus* (including MRSA/CoNS), *Streptococcus*
            (2) Most gram-negative bacteria, including *Acinetobacter*, ESBL-producing Enterobacterales, derepressed AmpC Enterobacterales, CRE, and *Stenotrophomonas*
            (3) Anaerobes, including *Bacteroides* and *Clostridium*
            (4) Atypicals
            (5) Does not cover *Pseudomonas*, *Providencia*, *Proteus, or Morganella*
         (d) PK
            (1) Wide volume of distribution: 7–10 L/kg
            (2) The intracellular distribution of tigecycline results in a decreased serum/tissue concentration ratio. This has led many clinicians to state that tigecycline is not the ideal drug for bloodstream infections. However, tigecycline has not been evaluated exclusively for the treatment of bloodstream infections. In a pooled analysis of eight

studies, patients with secondary bacteremia treated with tigecycline were compared with patients treated with other antibiotics. Overall, no significant differences in outcomes were seen. Despite these results, clinicians should exert caution with the use of tigecycline for bacteremia and should reserve tigecycline for pathogens when no other antibiotics are viable options.

(3) Primarily biliary elimination

(4) Urinary elimination is 8%–11%. The low urinary elimination limits tigecycline's role in treating UTIs. The use of tigecycline for treating multidrug-resistant UTIs has been reported only in case reports, with most reports showing treatment success. However, a recent evaluation of tigecycline for the treatment of KPC bacteriuria indicated a correlation with the subsequent development of tigecycline resistance. Without further data, tigecycline should not routinely be used for UTIs when other treatment options are available.

(5) Poor penetration into lung epithelial lining fluid, which is in contrast to high penetration into lung alveolar cells. This characteristic may partly explain the findings of a study evaluating tigecycline compared with imipenem for the treatment of hospital-acquired pneumonia. This study showed that tigecycline had a lower treatment success rate than imipenem. The difference in treatment success was mainly attributable to the significant differences in patients with ventilator-associated pneumonia. There was also a trend toward increased mortality in the subgroup of patients with ventilator-associated pneumonia.

(e) The FDA issued a safety warning in 2010 indicating a possible increased mortality risk associated with the use of tigecycline compared with other drugs used to treat a variety of other serious infections. This was compiled using several phase III studies in which tigecycline had been proven noninferior to other standard treatments. Subsequently, several other meta-analyses were published with conflicting results regarding tigecycline's increased mortality risk.

(f) Given tigecycline's possible shortcomings, it seems prudent to avoid the routine use of tigecycline in infections when other treatment options are available. However, tigecycline may be one of the few remaining antibiotic options for treating carbapenem-resistant pathogens. When tigecycline must be used because of limited treatment options, clinicians should consider administering combination therapy with other agents that have in vitro susceptibility.

(g) Resistance to tigecycline has been reported. Clinicians should seek confirmation from their microbiology laboratory regarding tigecycline sensitivity. Of note, CLSI currently has no recommendation for MIC breakpoint for tigecycline against *Acinetobacter* spp. The MIC breakpoint for sensitivity against Enterobacterales is 2 mcg/mL or less.

ii. Polymyxins:

(a) Colistin (polymyxin E)

(1) Mechanism of action: A cationic cyclic decapeptide that functions by displacing calcium and magnesium from the outer cell membrane, hence changing the permeability of the cell membrane to allow insertion of the molecule into the cell membrane. Once the molecule is inserted into the cell membrane, it disrupts the cell membrane integrity and subsequently leads to cell death.

(2) Spectrum of activity: Covers only gram-negative bacteria, including CRE. Does not cover *Proteus*, *Providencia*, *Burkholderia*, *Serratia*, or *Stenotrophomonas*

(3) First used in the United States in the 1960s but fell out of favor because of reports of nephrotoxicity and neurotoxicity

(4) Around 2000, with the emergence of CRE, colistin use was reconsidered, given the lack of treatment options.

(5) Dosing challenges
  (A) Different products provide different dosing recommendations.
  (B) Colomycin injection is the brand primarily used in Europe. Dosed in international units (IU).
  (C) Coly-Mycin is the brand primarily used in the United States. Dosing in colistin-based activity
  (D) 3 million IU of colistin is equal to about 100 mg of colistin-based activity.

(6) PK/PD
  (A) All colistin products, regardless of the dosing units, are administered as colistimethate, which is a prodrug. Colistimethate is hydrolyzed to the active drug colistin.
  (B) Colistimethate is excreted through renal clearance, whereas the active drug colistin is cleared by nonrenal pathways. Hence, renal dysfunction leads to a higher portion of colistimethate being present for hydrolysis into colistin, thus increasing the final active drug concentration.
  (C) PD parameter for maximal activity is area under the curve/MIC ratio.
  (D) In the 1960s, the dosing recommendations and PK/PD parameters were largely unknown because the methods for evaluations were drastically different from the current standards.
  (E) Recent PK/PD evaluations show that traditional dosing methods are probably insufficient to reach adequate serum concentrations to maximize PD target attainment.
  (F) Several studies have reported that a higher colistin dose is associated with significant improvements in clinical outcomes.
  (G) International consensus dosing recommendations
    - 300 mg colistin base activity loading dose.
    - 300-360 mg colistin base activity divided every 12 hours, with adjustments made based on renal function / renal replacement therapy.
  (H) Several ongoing investigations are evaluating the effects of high-dose colistin regimens and the utility of using a loading dose.
    - One study from South America is recruiting patients to evaluate the utility of a 200-mg loading dose.
    - One study reported a 300-mg loading dose regimen, followed by 150 mg every 12 hours. This study was non-comparative, but it reported high rates of clinical success.

(7) Because the PK/PD of colistin is unclear and little is known regarding the optimal dosing regimen, colistin should be reserved for infections in which other treatment options are not available. In such cases, it may be prudent to administer combination therapy. Furthermore, many in vitro studies have shown synergy between colistin and other antimicrobials.

(8) Resistance to colistin has been reported. In vitro studies also show that colistin resistance develops quickly, which may be another rationale for providing combination therapy. Clinicians should verify colistin susceptibility with their local microbiology laboratory.
  (A) Routine monitoring of colistin concentrations is currently infeasible.
  (B) According to PK data, an MIC of 2 mcg/mL or less should be considered sensitive.

(9) Empiric colistin therapy: In an analysis of the association between covering empiric antibiotics and mortality for infections caused by carbapenem-resistant gram-negative bacteria, the authors concluded that empiric use of colistin before pathogen identification, with or without a carbapenem, was not associated with survival.

(b) Adverse reaction: Nephrotoxicity

(1) Nephrotoxicity

(A) 0%–45% reported in recent literature, depending on the definitions used for renal dysfunction

(B) In general, seems to be dose-dependent

(C) Usually reversible, with few cases leading to a prolonged need for renal replacement therapy

(2) Neurotoxicity

(A) Ranging from paresthesia to apnea

(B) Incidence of 8%–27% reported in historical studies

(C) Mentioned only in case reports in the current era of colistin use

(c) Polymyxin B:

(1) Mechanism of action, spectrum of activity, and adverse reactions similar to those of colistin

(2) Available in the United States but not in Europe and Australia

(3) PK/PD

(A) Administered as an active drug

(B) PD targets similar to those of colistin

- Similar unknowns regarding best dosing regimen to achieve PD parameters
- Manufacturer-recommended dosing: 1.5–2.5 mg/kg/day divided every 12 hours. Recommends renal dose adjustment, but recent studies suggest minimal renal clearance.

(C) International consensus dosing recommendations

- Loading dose of 2–2.5 mg/kg total body weight
- 1.25–1.5 mg/kg total body weight every 12 hours

(d) International consensus guidelines for the optimal use of polymyxins

(1) Use therapeutic drug monitoring, when possible (see Pharmacokinetics/Pharmacodynamics chapter for further information regarding colistin therapeutic drug monitoring).

(2) Recommend hospitals have access to both polymyxins

(A) Polymyxin B preferred for routine systemic use because of superior and more predictable PK

(B) Colistin preferred agent for UTIs

(C) Recent systematic review suggests that polymyxin B is associated with less acute kidney injury than colistin.

iii. Ceftazidime/avibactam

(a) Avibactam is a new β-lactamase inhibitor approved by the FDA in 2015.

(b) Spectrum of activity: Broad gram-negative activity, including multidrug-resistant *Pseudomonas* and Enterobacterales. Adding avibactam allows coverage against KPC-producing bacteria, together with coverage against other β-lactamases (OXA, CTX-M, AmpC). Minimal coverage against metallo-β-lactamase-expressing strains, *Acinetobacter* spp., gram-positive, and anaerobes.

(c) FDA approved for the treatment of complicated intra-abdominal infection and complex UTIs. However, most clinicians will reserve its coverage for difficult-to-treat pathogens with minimal coverage options, such as KPC-producing Enterobacterales.

(d) An in vitro study that included 120 KPC-producing pathogens showed good activity with ceftazidime/avibactam.

(e) A recent multicenter-observational, propensity score-weighted study comparing ceftazidime/avibactam with colistin as the initial treatment for CRE showed significant improvements in mortality. These findings require confirmation in a randomized controlled study.

(f) Study evaluating compassionate use of ceftazidime/avibactam as a second-line agent compared with a matched cohort of patients with CRE bacteremia treated with a different agent illustrated significant improvements in mortality (36.5% vs. 55.8%, $p=0.005$).

(g) No major adverse effects were seen with ceftazidime/avibactam in phase II and phase III studies.

(h) Currently, the average wholesale price for ceftazidime/avibactam is about $1000 per day with normal dosing. This is similar to meropenem/vaborbactam but considerably more expensive than other β-lactams.

iv. Meropenem/vaborbactam

(a) Vaborbactam, which alone has no antimicrobial activity, is a novel cyclic boronic acid-based β-lactamase inhibitor that potentiates the activity of meropenem.

(b) Spectrum of activity: Broad gram-negative activity, including multi-drug resistant Enterobacterales, and remains stable in the presence of ESBLs and AmpC β-lactamases. Vaborbactam is a potent inhibitor of class A carbapenemases, including KPC and class A and C β-lactamases. It is not found to expand coverage to carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, or *Stenotrophomonas maltophilia*.

(c) FDA-approved in 2017 for complicated UTIs. However, most clinicians reserve its coverage for difficult-to-treat pathogens with minimal coverage options, such as KPC-producing Enterobacterales.

(d) A recent multicenter, randomized, prospective, open-label, comparative trial evaluated the efficacy of meropenem/vaborbactam to best available therapy (including mono- or combination therapy with polymyxin B or colistin, carbapenems, aminoglycosides, tigecycline, or ceftazidime/avibactam) for the management of complicated UTI, healthcare-associated pneumonia, ventilator-associated pneumonia, bloodstream infections, and complicated intra-abdominal infections. Meropenem/vaborbactam demonstrated improved efficacy and decreased adverse events compared to best available therapy. Of note, only one patient received ceftazidime/avibactam; therefore, no conclusions can be drawn regarding comparative efficacy between these two agents.

v. Imipenem/cilastatin/relebactam

(a) Cilastatin is a dehydropeptidase-1 inhibitor that prevents inactivation of imipenem by renal dehydropeptidase-1.

(b) Relebactam is a non-β-lactam β-lactamase inhibitor that is active against class A β-lactamases. Compared to avibactam, relebactam has less inhibitory activity against OXA-48, and neither inhibitor is active against metallo-β-lactamases.

(c) FDA-approved in 2019 for complicated UTIs, intra-abdominal infections, and health care-associated/ventilator-associated pneumonia. However, most clinicians reserve its coverage for difficult-to-treat pathogens with minimal coverage options, such as KPC-producing Enterobacterales.

(d) In vitro studies have demonstrated that relebactam, when added to imipenem/cilstatin, restores activity against imipenem nonsusceptible strains that produce KPC.

- (e) A recent multicenter, randomized, double-blind, comparator controlled trial compared the efficacy and safety of imipenem/relebactam and colistin combined with imipenem/cilastatin in patients with imipenem-resistant gram-negative bacterial infections (health care-associated/ventilator-associated pneumonia, complicated intra-abdominal infections, or complicated UTI). Clinical response rates were higher for imipenem/relebactam compared to imipenem/colistin.

vi. Cefiderocol

- (a) Novel siderophore cephalosporin with a unique mechanism of action that confers activity against a broad spectrum of resistant gram-negative bacteria, including Enterobacterales, *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*. It has no clinically relevant in vitro activity against most gram-positive bacteria and anaerobes.
- (b) Cefiderocol is able to chelate ferric ions and use bacterial iron transport systems, which has been called a "Trojan Horse" strategy and translates to higher concentrations of susceptible gram-negatives in the periplasmic space.
- (c) Due to the cephalosporin/catechol structure, it has increased stability against hydrolysis by clinically relevant β-lactamases, including serine (including KPCs and OXA-48) and metallo-β-lactamases. Given the use of the iron transport pathway, cefiderocol does not require classic β-lactam porin channels to penetrate the cells, and therefore, retains activity in the presence of porin channel mutations and remains unaffected by common efflux pumps present in Enterobacterales.
- (d) FDA-approved in 2019 for complicated UTIs.
- (e) In vitro studies have demonstrated excellent activity of cefiderocol against class A, B, and D CRE.
- (f) A multicenter, randomized, open-label study of cefiderocol compared to best-available therapy for the treatment of severe infections (hospital-acquired pneumonia, ventilator-associated pneumonia, complicated UTI, bloodstream infection, and sepsis) caused by carbapenem-resistant gram-negative pathogens. All-cause mortality versus other antibiotics in critically ill patients was higher in the cefiderocol arm. The cause of higher mortality was not established.

vii. Eravacycline

- (a) Novel fluorocycline of the tetracycline class with a similar structure to tigecycline, escaping many resistance mechanisms seen in other tetracyclines
- (b) FDA-approved in 2018 for complicated intra-abdominal infections. It was investigated for use with UTIs, but outcomes were not favorable.
- (c) Demonstrated in vitro activity against most gram-positive and gram-negative pathogens, including CRE and *Acinetobacter*, and anaerobes. It lacks activity against *Pseudomonas.*
- (d) Low oral bioavailability; therefore, only IV formulation is FDA-approved.
- (e) Randomized, double-blind, multicenter trial found that eravacycline was noninferior to ertapenem for the management of complicated intra-abdominal infections.

viii. Omadacycline

- (a) Omadacycline is an aminomethylcycline antibiotic in the tetracycline class escaping many resistance mechanisms seen in other tetracyclines.
- (b) FDA approved in 2018 for community-acquired bacterial pneumonia and SSIs
- (c) Has activity against most gram-positive and gram-negative pathogens, including ESBL-producing isolates, *Acinetobacter, Stenotrophomonas*, anaerobes, and atypicals. It lacks activity against *Pseudomonas.*
- (d) Available as an injectable and oral
- (e) Randomized, double-blind, multicenter trial found that eravacycline was noninferior to moxifloxacin for the management of community-acquired bacterial pneumonia.

ix. Sulbactam/durlobactam
   (a) Only agent developed for the treatment of carbapenem-resistant *Acinetobacter baumanii* (CRAB)
   (b) Sulbactam has intrinsic activity to Acinetobacter spp., whereas durlobactam had broad-spectrum activity to class A, C, and D β-lactamases.
      (1) Antimicrobial activity of sulbactam is because of its ability to inactivate penicillin-binding protein.
      (2) Durlobactam is a non–β-lactam/β-lactamase inhibitor with expanded coverage of class D β-lactamases.
   (c) FDA approved in 2023 for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia
   (d) A randomized multicenter trial showed sulbactam/durlobactam administered in combination with imipenem-cilastatin was noninferior to colistin for the primary efficacy end point of 28-day all-cause mortality for the treatment of CRAB.

x. Combination therapy
   (a) Several retrospective studies suggested that the use of combination therapy is warranted for the treatment of CRE, particularly a regimen involving colistin, tigecycline, and a carbapenem. Interpreting these studies is difficult. Many were noninterventional, hence leading to the evaluation of many treatment regimens. The increased ratio of the number of treatment regimens to the number of patients substantially increases the risk of spurious findings. If no optimal therapy exists for a patient, combination therapy may be considered. These therapies include scenarios in which the carbapenem MIC may be slightly elevated or in which therapies with suboptimal PK/PD (i.e., colistin and tigecycline) are used.
   (b) A recent retrospective study that evaluated the role of combination therapy for carbapenem-resistant gram-negative pathogens showed that combination therapy with several agents, all of which had in vitro sensitivity, led to improvements in outcomes. In contrast, combination therapy with several agents, not all of which had in vitro sensitivity, did not lead to improvements.
   (c) Several case reports recommend considering combining ertapenem with another carbapenem for the treatment of carbapenem-resistant pathogens. This approach takes advantage of the increased affinity for ertapenem seen in vitro with carbapenemases. Hence, administering ertapenem as a sacrificial carbapenem may allow a different carbapenem to exert its effects. Recent systematic review identified 171 patients who were treated with this combination carbapenem strategy, and found clinical and microbiological success reported in 70% of patients. However, this practice requires further testing; hence, it cannot currently be recommended.
   (d) If using polymyxin, combination therapy with another agent that has a susceptible MIC is recommended.

4. Multidrug-resistant *Pseudomonas*
   a. Resistance mechanisms seen with *Pseudomonas aeruginosa* are unpredictable. The presence of several mechanisms, including β-lactamases, porin loss, efflux pump, and alteration of target proteins, complicates treatment options.
   b. Clinical approach usually entails empiric coverage with a β-lactam, which has the best local in vitro activity against *Pseudomonas*, with or without a second antipseudomonal agent. Therapy could be de-escalated to a monotherapy with the narrowest spectrum on availability of AST results.
   c. Ceftolozane/tazobactam is a novel β-lactam/β-lactamase inhibitor antimicrobial with enhanced activity against *P. aeruginosa*.

- i. Ceftolozane is a novel fifth-generation cephalosporin.
- ii. Spectrum of activity: Gram-negative organisms, including *P. aeruginosa*. Activity includes coverage against ESBL and AmpC β-lactamase–producing organisms. Limited gram-positive and anaerobic coverage. Among multidrug-resistant and extended drug–resistant *Pseudomonas*, ceftolozane/tazobactam retains good activity, with its MIC_{90} still below the MIC breakpoint for resistant, as determined by the FDA.
- iii. FDA approved for the treatment of complicated intra-abdominal infection, complicated UTI, and hospital-acquired and ventilator-associated pneumonia. However, clinically, its coverage will most likely be reserved for resistant pseudomonal infections. A recent study concluded that high-dose ceftolozane/tazobactam (3 g every 8 hours) was noninferior to meropenem in the treatment of nosocomial pneumonia. Twenty-eight day mortality, clinical response, and adverse reactions were similar between groups.

d. Aminoglycosides
- i. CLSI aminoglycoside breakpoint revisions
  - (a) CLSI breakpoints are not recognized by the FDA.
- ii. Recommend tobramycin 7 mg/kg every 24 hours if expanding coverage for *Pseudomonas.*
  - (a) Gentamicin is no longer recommended for *Pseudomonas.*
  - (b) Amikacin may be considered if being used for a urinary source.

5. MRSA

a. MRSA is a significant cause of both community- and hospital-acquired infections.

b. Skin and soft tissue infections
- i. Community-acquired MRSA often presents as a skin and soft tissue infection.
- ii. Cutaneous infections and abscesses are best treated with adequate drainage.
- iii. Antibiotics are usually not necessary unless the patient does not respond to drainage, has extensive disease, or has signs and symptoms of systemic infection.
- iv. Antibiotic treatment choices for community-acquired MRSA cutaneous and skin infections include trimethoprim/sulfamethoxazole, clindamycin, and tetracycline.

c. MRSA bacteremia and endocarditis
- i. Can be treated with either vancomycin or daptomycin
- ii. In a study of patients with right-sided endocarditis, daptomycin was noninferior to vancomycin. Of interest, treatment response was poor with both therapies, with only about 40% in each group meeting the primary outcome of treatment success 42 days after the end of therapy. Daptomycin was dosed at 6 mg/kg in this study.
- iii. Some experts recommend giving higher daptomycin doses (8–10 mg/kg) to optimize the PD target attainment for daptomycin. Daptomycin resistance in *S. aureus* has been reported. A correlation appears to exist between intermediate sensitivity to vancomycin, thought to be caused by a thickened cell wall–limiting penetration, and decreased susceptibility to daptomycin. Currently, the daptomycin breakpoint MIC for MRSA is 1 mcg/mL or less.
- iv. Several investigations have also evaluated daptomycin compared with vancomycin for MRSA bacteremia when the vancomycin MIC was greater than 1 mcg/mL. Although these investigations showed outcome benefit associated with daptomycin use, the studies have several limitations, which may limit their applicability.
  - (a) Retrospective analyses
  - (b) Daptomycin was usually used as definitive therapy after an initial course of vancomycin.
  - (c) Daptomycin use in one study was associated with a significantly higher rate of infectious diseases consultation, which may have other treatment implications.
  - (d) Given study limitations, the routine use of daptomycin for MRSA infections when the vancomycin MIC is greater than 1 mcg/mL cannot be recommended.

        - (e) The 2011 IDSA guidelines for the treatment of MRSA state that the treatment of isolates with a vancomycin MIC of 2 mcg/mL or less should be determined by the patient's response to vancomycin, independent of the MIC.
- d. MRSA pneumonia
    - i. Community-acquired MRSA pneumonia can be treated with either vancomycin or linezolid. Clindamycin can be considered if the strain is susceptible.
    - ii. Community-acquired MRSA infections may be associated with the presence of Panton-Valentine leukocidin, which is a two-component staphylococcal membrane toxin that targets leukocytes. This toxin has been linked with severe infections, necrotizing pneumonia, and abscess formation. Theoretically, clindamycin and linezolid, being ribosomal subunit and protein synthesis inhibitors, may attenuate the amount of toxin production.
    - iii. A randomized controlled study comparing linezolid to vancomycin included patients with hospital-acquired pneumonia and ventilator-associated pneumonia who had a baseline respiratory culture positive for MRSA.
        - (a) Vancomycin was dosed by weight and adjusted locally according to trough levels.
        - (b) This was a noninferiority study with nested superiority criteria where the primary end point was clinical response at the end of the study.
        - (c) Clinical response was defined as resolution of signs of pneumonia with no further need for other antibiotics.
        - (d) Study met both the noninferiority and the superiority criteria with respect to clinical response and microbiological clearance.
        - (e) Study may have been confounded by less than 50% of patients reaching vancomycin target concentrations by day 3 and the vancomycin patients having a slightly higher rate of baseline bacteremia.
        - (f) No difference in mortality was seen.
        - (g) Many clinicians interpret the results from this study as suggesting that either vancomycin or linezolid can be considered for the treatment of MRSA pneumonia.
- e. Updates to vancomycin dosing and monitoring
    - i. Consensus guidelines for therapeutic monitoring of vancomycin were published in 2020.
    - ii. AUC24 of 400–600 mg/hour/L is recommended target to improve clinical efficacy and patient safety. For most isolates, an MIC of 1 mg/L can be assumed.
    - iii. Trough targets are no longer recommended for patients with serious MRSA infections.
    - iv. Bayesian dosing is the recommended method for dosing adjustments. Bayesian dosing does not require steady-state vancomycin concentrations for early determination of AUC target attainment.
- f. Novel agents for the treatment of MRSA
    - i. Tedizolid is FDA-approved for the treatment of bacterial skin and skin structure infection.
        - (a) Antimicrobial class: Oxazolidinone
        - (b) Spectrum of activity: Gram-positive pathogens including MRSA, vancomycin-resistant enterococci, vancomycin-resistant staphylococci, drug-resistant *S. pneumoniae*, and linezolid-resistant gram-positive pathogens
        - (c) PK and dosing
            - (1) Bioavailability 91% – Can be administered as a parenteral solution or oral tablets
            - (2) Half-life: 12 hours
            - (3) Dosing: 200 mg once daily
        - (d) Studies:
            - (1) Tedizolid once daily for 6 days was compared with linezolid twice daily for 10 days for the treatment of acute bacterial skin and skin structure infection and was found to be noninferior.

        (2) Tedizolid once daily for 7 days was compared with linezolid twice daily for 10 days for the treatment of gram-positive hospital-acquired or ventilator-associated bacterial pneumonia and was found to be noninferior for day 28 all-cause mortality, but did not meet noninferiority for clinical response at test of cure.
    (e) Application: Place in therapy among critically ill patients is limited, but tedizolid use may be warranted in patients that experience linezolid-associated adverse effects.

ii. Ceftaroline
    (a) Antimicrobial class: Fifth-generation cephalosporin
    (b) Spectrum of activity: Enterobacterales (similar to third-generation cephalosporins) and gram-positive pathogens, including MRSA, drug-resistant *S. pneumoniae*, and vancomycin-intermediate and vancomycin-resistant staphylococci
    (c) PK and dosing
        (1) Activity against MRSA mediated through enhanced affinity to penicillin-binding-protein 2a
        (2) Half-life: 2.7 hours
        (3) Excretion: 88% urine
        (4) Dosing:
            (A) 600 mg intravenously every 12 hours is the FDA label-approved dosing. Reports of using 600 mg intravenously every 8 hours for severe infections
            (B) Adjustments necessary for patients with renal impairment
    (d) Studies:
        (1) Evaluated in a noninferiority trial compared with ceftriaxone, both in conjunction with clarithromycin, for the treatment of community-acquired bacterial pneumonia. Results indicated noninferiority, with numerically higher cure rates in those randomized to ceftaroline. Clinical response by day 4 of therapy was also higher in the ceftaroline group.
        (2) Evaluated in a noninferiority trial compared with vancomycin plus aztreonam for the treatment of skin and skin structure infection. Ceftaroline cure rates were within the *a priori*–determined margin, thus satisfying the criteria for noninferiority.
    (e) Application:
        (1) FDA approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia
        (2) Despite its FDA approvals, the main role of ceftaroline is the availability of an additional agent with activity against MRSA. May be an option when vancomycin therapy is suboptimal and other treatment options may lead to unwanted adverse effects. May also be a reasonable option for the treatment of community-acquired pneumonia in institutions where community-acquired MRSA is common and for the salvage treatment of MRSA bacteremia

iii. Ceftobiprole
    (a) Cephalosporin antibiotic
    (b) FDA approved in 2024 for the treatment of *S. aureus* bacteremias (including those with right-sided endocarditis), SSIs, and community-acquired pneumonia
    (c) Has activity against MRSA and Enterobacterales (similar to third-generation cephalosporins)
    (d) Studies
        (1) Showed noninferiority to daptomycin plus aztreonam for MRSA bacteremia
        (2) Showed noninferiority to vancomycin plus aztreonam for SSIs
        (3) Showed noninferiority to ceftriaxone plus optional linezolid for community-acquired pneumonia

Patient Case

6. A 72-year-old woman with a history of end-stage renal disease is admitted to the medical ICU with signs and symptoms of sepsis. Blood cultures are obtained in which two of two bottles grow gram-positive cocci. The patient is initiated on vancomycin, and her tunneled dialysis catheter is removed. On day 4 of therapy, the blood cultures are finalized to be MRSA with the following antibiotic susceptibility results: oxacillin greater than 4 mcg/mL – R; vancomycin 2 mcg/mL – S; daptomycin 0.5 mcg/mL – S; and linezolid 1 mcg/mL – S. A transthoracic echocardiogram is obtained, which reveals echodensities on the mitral valve. The patient will be treated medically with antibiotics for 4–6 weeks. The patient's repeat blood cultures are currently no growth. Her vital signs and laboratory values are as follows: blood pressure 150/90 mm Hg, heart rate 88 beats/minute, temperature 100.2°F, WBC 11 x 10^3 cells/mm^3, and lactate 1.1 mmol/L. Which is the most appropriate treatment regimen?
   A. Change vancomycin to linezolid 600 mg every 12 hours.
   B. Add gentamicin and rifampin to vancomycin.
   C. Change vancomycin to daptomycin 6 mg/kg every 48 hours.
   D. Continue vancomycin, and target a trough level of 15–20 mcg/mL.

VII. IMMUNOCOMPROMISED PATIENTS

A. Febrile Neutropenia
   1. Definition
      a. Fever: A single temperature of 101°F (38.3°C) or greater orally or a temperature of 100.4°F (38.0°C) or greater orally for more than 1 hour
      b. Neutropenia: Less than 500 neutrophils/mm^3 or less than 500 neutrophils/mm^3 during the next 48 hours
   2. Risk stratification
      a. Patients presenting with febrile neutropenia undergo initial risk assessment for serious complications to determine appropriate treatment. Depending on risk, treatment of patients can vary in administration (intravenous vs oral antimicrobials), duration, and setting (outpatient vs hospital).
      b. Patients are stratified into high- vs low-risk categories on the basis of clinical criteria, including duration of neutropenia, ANC at presentation, presence of comorbidities, presence of renal and/or hepatic dysfunction, medication use, and history of febrile neutropenia.
      c. The Multinational Association of Supportive Care in Cancer (MASCC) score is a tool used for risk stratification.
         i. The MASCC score assigns values to patient age, history, outpatient vs inpatient status, severity of fever and neutropenia, and presence of comorbidities. Scores of 21 or greater equate to low-risk status, whereas scores of less than 21 signal high-risk status.
      d. Patients considered at low risk have good performance status, few to no comorbidities, adequate end-organ function, and an expected duration of neutropenia less than 7 days.
      e. Patients considered at high risk present with an ANC of less than 100 neutrophils/mm^3, duration of neutropenia expected to last longer than 7 days, end-organ dysfunction, and comorbidities.
   3. Initial therapy should include monotherapy with an intravenous antipseudomonal β-lactam (i.e., cefepime, piperacillin/tazobactam, meropenem, imipenem). Patients with type 1 hypersensitivity should be treated with either ciprofloxacin or aztreonam plus vancomycin.

4. Consider dual gram-negative therapy (fluoroquinolone or aminoglycosides) in patients with shock or if antimicrobial resistance is suspected.
5. Consider adding vancomycin to gram-negative therapy in patients with shock, suspected catheter-related infection, skin and soft tissue infection, pneumonia, and/or hemodynamic instability. Gram-positive therapy can be discontinued in 48–72 hours if no evidence of gram-positive infections is discovered.
6. Modifications to initial antibiotic choices should be considered for patients with worsening clinical status or if patients' microbiological data warrant change.
7. Unexplained persistent fever in an otherwise clinically stable patient rarely warrants an escalation in therapy. Persistent fevers for 4–7 days after initiation of antibacterial agents should warrant consideration for empiric antifungal coverage in those who have persistent neutropenia.
8. Initial antimicrobials should be de-escalated or escalated in documented infections depending on in vitro susceptibility. Treatment of febrile neutropenia is necessary until the patient is afebrile for at least 48 hours, is hemodynamically stable with resolution of neutropenia (ANC greater than 500 cells/mm^3), and has negative blood cultures. For patients with documented infections, the treatment duration is decided by the organism and infection site; treatment should always continue until neutrophil resolution (ANC greater than 500 cells/mm^3).
9. Patients with hemodynamic instability should have their initial antibiotic regimen escalated to include coverage for resistant bacteria and fungi.
10. Hematopoietic growth factors should not be used for the treatment of febrile neutropenia. Prophylactic use of hematopoietic growth factors should be considered for patients with a high anticipated risk of febrile neutropenia (20% or greater).

B. Solid Organ Transplantation
   1. Epidemiology
      a. Hospital-acquired bacterial infections are the most common types of infections in SOT recipients.
      b. 50%–75% of SOT recipients will experience an infection within the first year after transplantation.
      c. Posttransplant infections may contribute to graft dysfunction and reduce long-term survival, and they have been associated with prolonged LOS and cost of care.
      d. An analysis of 60,000 renal transplant recipients found that infections were the second leading cause of death.
   2. General risk factors for infections
      a. Excessive use of antibiotics before transplantation: With the use of prophylactic antimicrobials in the pretransplant period, many transplant recipients are experiencing resistant pathogens in the posttransplant period.
      b. Infections are most common in the first 6 months after transplantation, with different pathogens presenting after various durations of immunosuppression. See Figure 3. OIs are rare in the first month after transplantation because the full effects of immunosuppression are not yet present. Fungal and viral infections experienced during the first month after transplantation are usually donor derived.
      c. Duration of hospitalization after transplantation
      d. Renal dysfunction
      e. Several acute rejection episodes
   3. General clinical approach for infectious diseases issues in critically ill SOT recipients
      a. Be cognizant of the patient's transplant timeline, particularly with respect to possible OIs, pretransplant risk factors, immune status, intensity of immunosuppressive therapy, prophylactic regimens, and recent treatments of rejection.
      b. Have a high clinical suspicion for OIs.

c. Severe infections sometimes warrant a reduction in maintenance immunosuppression. Consult with the transplant team regarding plans for maintenance immunosuppression.
d. Be aware of the many drug interactions between immunosuppressants and antimicrobials.

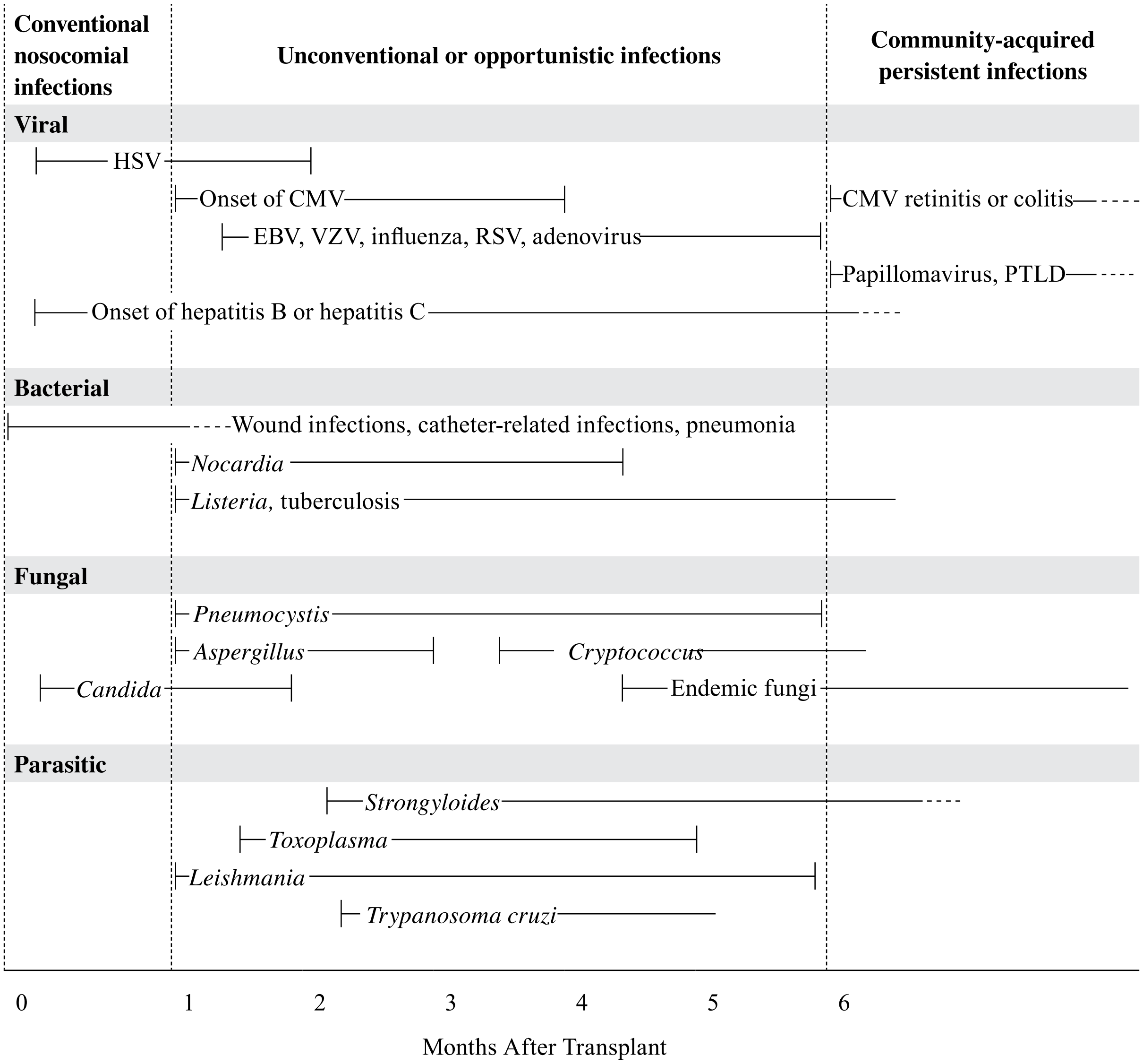

Figure 3. Usual sequence of infections after organ transplantation.[a]

[a]Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted lines indicate periods of continued risk at a reduced level.

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; PTLD = posttransplant lymphoproliferative disease; RSV = respiratory syncytial virus; VZV = varicella-zoster virus.

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VIII. HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNE DEFICIENCY SYNDROME IN CRITICALLY ILL PATIENTS

A. Diagnosis
   1. Isolated $CD4^+$ lymphopenia has occurred in critically ill patients without HIV disease.
      a. Differential diagnosis of $CD4^+$ lymphopenia
         i. Idiopathic
         ii. Common variable immunodeficiency
         iii. Corticosteroid administration
         iv. Circadian rhythm
         v. Hematologic malignancies
         vi. Critical illness
   2. Patients with traditional HIV risk factors, isolated $CD4^+$ lymphopenia, or AIDS-defining OIs who have not been given a diagnosis should receive HIV serologic testing. See Table 10 for AIDS-defining conditions.

B. Presentation for HIV-Associated Acute Illness
   1. Changing prescribing patterns in highly active antiretroviral therapy (HAART) and improvements in care have changed the landscape of ICU admissions associated with HIV. Although rates of ICU admissions among HIV-positive patients have remained stable over time, the rationale for ICU admission has shifted from respiratory distress associated with pneumocystic pneumonia to other sepsis etiologies, neurologic disorders, and other end-organ dysfunctions.
   2. See Table 11 for the management and prophylaxis of commonly occurring OIs in critically ill patients.

C. Management of HAART Therapy
   1. Treatment-naive patient
      a. Initiation of HAART in an ICU may be deterred by factors such as lack of enteral access, inability to assess the patient’s willingness to commit to therapy, and high probability of interruptions in therapy because of surgical interventions.
      b. Immune reconstitution inflammatory syndrome
         i. Unexpected worsening of existing OI or unmasking of previously unrecognized illness associated with recent HAART initiation
         ii. Recovery of immune response leading to a proinflammatory cytokine storm
         iii. Risk factors
            (a) Presence of disseminated disease or high antigen load
            (b) High baseline HIV viral load
            (c) Rapid response to antiretroviral therapy
         iv. Evidence does not suggest that early administration of HAART (at the onset of an AIDS-defining OI) is associated with a higher incidence of immune reconstitution inflammatory syndrome.
         v. In general, early and continued administration of HAART is associated with improved outcomes, particularly in patients with OI. For patients with severe symptoms associated with immune reconstitution inflammatory syndrome (requiring vasopressors or intubation) consider the adjunctive use of prednisone.
   2. Patient receiving HAART regimen
      a. Considerations: Availability of drug formulations conducive to ICU administration; food requirements; dose adjustments associated with renal or hepatic impairment; new drug interactions; possible interruptions in therapy

  b. In general, if one of the antiretroviral therapies has to be discontinued, all of the therapies should be discontinued to decrease the promotion of resistance caused by the suboptimal suppression of viral replication. Rationale: Nonnucleoside reverse transcriptase inhibitors (NNRTIs) have long half-lives (as long as 3 weeks); therefore, if NNRTIs are discontinued at the same time as other antiretrovirals with shorter half-lives, there will be a period of functional NNRTI monotherapy. May consider continuing antiretrovirals with shorter half-lives, if possible, for 1–2 weeks to minimize selection of NNRTI resistance.
  c. Possible ICU drug interactions – See Table 12.

3. HAART-associated adverse drug reactions
   a. Newer generations of HAART regimens are generally well tolerated; however, many patients still receive older HAART therapy.
   b. Many of the HAART-associated adverse effects have no specific treatment; therefore, early recognition and prompt discontinuation of the offending agent is crucial.
   c. Lactic acidosis
      i. Two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (e.g., lamivudine and tenofovir) remain the backbone of many HAART regimens.
      ii. NRTIs are associated with a variety of mitochondrial toxicities.
      iii. Older NRTIs, such as zidovudine, stavudine, and didanosine, have been associated with lactic acidosis.
      iv. Symptoms: Fatigue, malaise, nausea, vomiting, abdominal pain, hepatomegaly
      v. Management: Supportive therapy and discontinuing the potential offending agent
   d. Abacavir hypersensitivity
      i. Symptoms: Fever, rash, gastrointestinal (GI) symptoms
      ii. Reaction associated with the presence of the *HLA-B*5701* allele, which has an 8% prevalence among whites in North America. Genetic screening for this allele is recommended.
      iii. Management: Supportive care and discontinuing agent, with rechallenge contraindicated because of the possibility of life-threatening hemodynamic compromise
   e. Other HAART-associated significant adverse effects:
      i. Nevirapine hypersensitivity: Rash (may progress to Stevens-Johnson syndrome), fever, hepatotoxicity
      ii. Raltegravir-associated rhabdomyolysis
      iii. Tipranavir-associated hepatotoxicity and intracranial hemorrhage
      iv. Protease inhibitor–associated pancreatitis

D. Management and Prophylaxis of HIV-Associated Infections: See Table 10.

Table 10. AIDS-Defining Conditions

Bacterial infections, multiple/recurrent (children < 13 yr)
Candidiasis: Bronchi, trachea, or lungs
Candidiasis: Esophageal
Cervical cancer: Invasive (> 13 yr)
Coccidioidomycosis: Disseminated or extrapulmonary
Cryptococcosis: Extrapulmonary
Cryptosporidiosis: Chronic intestinal (for > 1 mo)
Cytomegalovirus disease (other than the liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy: Related to HIV
Herpes simplex: Chronic ulcer(s) (for > 1 mo); bronchitis, pneumonitis, or esophagitis
Histoplasmosis: Disseminated or extrapulmonary
Isosporiasis: Chronic intestinal
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex (children < 13 yr)
Lymphoma: Burkitt (or equivalent term)
Lymphoma: Immunoblastic (or equivalent term)
Lymphoma: Primary or brain
Mycobacterium avium complex or *M. kansasii*: Disseminated or extrapulmonary
M. tuberculosis: Any site (pulmonary or extrapulmonary)
Mycobacterium: Other species or unidentified species; disseminated or extrapulmonary
P. jiroveci pneumonia
Pneumonia: Recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia (recurrent)
Toxoplasmosis of brain
Wasting syndrome caused by HIV

Patient Case

7. A 46-year-old man is admitted to the medical ICU for diabetic ketoacidosis. The patient has a history of insulin-dependent diabetes, is HIV positive, and has cryptococcal meningitis. His current HAART regimen consists of atazanavir, ritonavir, tenofovir, and emtricitabine, which is continued on admission to the ICU. The patient's CD4$^+$ count is 85 cells/mm^3. The patient's diabetic ketoacidosis is well controlled, and he is ready to be discharged from the ICU. Before discharge, the patient is noted not to be on any prophylaxis against OIs. Which prophylactic regimen would be most appropriate for the patient?
   A. Azithromycin 1200 mg once weekly and trimethoprim/sulfamethoxazole 1 double-strength (DS) tablet thrice weekly.
   B. Fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet daily.
   C. Azithromycin 1200 mg once weekly and fluconazole 200 mg daily.
   D. Fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet thrice weekly.

Table 11. AIDS-Associated OIs and Their Respective Prophylactic and Treatment Options

OI/$CD4^+$ Threshold for Prophylaxis	**Prophylaxis Option**	**Treatment Option**
P. jiroveci: < 200 cells/mm^3 and/or CD4 cell percentage < 14%	Preferred: TMP/SMX[b] 1 DS PO daily *or* TMP/SMX[b] 1 SS PO daily Alternatives Dapsone[a] PO 100 mg/day Pentamidine 300 mg inhalation once monthly TMP/SMX 1 DS PO TIW Atovaquone PO 1500 mg/day	Preferred: TMP/SMX[b] 15–20 mg/kg PO/IV divided q6–8hr x 21 days *plus* prednisone 40 mg PO q12hr x 5 days; 40 mg/day x 5 days; 20 mg/day x 11 days (if Pao_2 < 70 mm Hg or alveolar-arterial O_2 gradient > 35) (IV methylprednisolone could be administered at 75% of the corresponding oral prednisone dose) Alternatives: Pentamidine[b] IV 4 mg/kg/day Clindamycin 600–900 mg PO/IV q6–8hr + primaquine[a] PO 30 mg/day (base) Atovaquone 750 mg PO q12hr – mild disease
Toxoplasmosis: < 100 cells/mm^3 and *Toxoplasma* IgG positive	Preferred: TMP/SMX 1 DS PO daily Alternatives: Dapsone[a] PO 50 mg/day + (pyrimethamine 50 mg PO + leucovorin 25 mg PO) once weekly TMP/SMX 1 DS PO TIW	Preferred: Pyrimethamine[b] 200 mg PO x 1; then 50–75 mg/day + sulfadiazine[b] 1000–1500 mg PO q6hr + leucovorin PO 10–20 mg/day x 6 wk Alternatives: Pyrimethamine[b] 200 mg PO x 1; then 50–75 mg/day + clindamycin 600–900 mg PO/IV q8hr + leucovorin PO 10–20 mg/day Pyrimethamine[b] 200 mg PO x 1; then 50–75 mg/day + atovaquone 1500 mg PO BID + leucovorin PO 10–20 mg/day
Mycobacterium avium complex: < 50 cells/mm^3 *M avium* complex: < 50 cells/mm^3 AND not receiving antiretroviral therapy (ART), remain viremic while treated with ART, or have no options for a fully suppressive ART regimen	Preferred: Azithromycin 1200 mg once weekly *or* Clarithromycin 500 mg q12hr *or* Azithromycin 600 mg twice weekly Alternatives: Rifabutin[c] 300 mg/day	Preferred: At least two drugs: Clarithromycin 500 mg PO BID *or* azithromycin 600 mg/day *plus* ethambutol[b] PO 15–25 mg/kg/day Additional agents (consider depending on susceptibility testing, severe disease, or low $CD4^+$ count) Rifabutin[c] PO 300 mg/day Amikacin[b] IV 10–15 mg/kg/day fluoroquinolones (moxifloxacin PO/IV 400 mg/day or levofloxacin[b] PO/IV 500 mg/day)

Table 11. AIDS-Associated OIs and Their Respective Prophylactic and Treatment Options *(continued)*

OI/CD4$^+$ Threshold for Prophylaxis	Prophylaxis Option	Treatment Option
Mycobacterium tuberculosis: Primary prophylaxis not indicated	Latent infection treatment Preferred: Isoniazid (INH) PO 300 mg/day + pyridoxine PO 50 mg/day Alternatives: INH 900 mg PO twice weekly + pyridoxine 100 mg PO twice weekly	Active infection treatment Preferred: Rifampin^c PO/IV 600 mg/day + INH PO 300 mg/day + pyrazinamide^b PO 20–25 mg/kg/day + ethambutol^b PO 15–25 mg/kg/day
Cryptococcosis: Primary prophylaxis not indicated Secondary prophylaxis may be considered < 100 cells/mm^3	Secondary prophylaxis: Fluconazole 200–400 mg/day	Preferred: Induction therapy x 2 wk: Liposomal amphotericin IV 3-4 mg/kg/day + flucytosine^b PO 25 mg/kg q6hr Alternatives: Induction x 2 wk: 1. Amphotericin B IV 0.7–1 mg/kg/day + flucytosine^b PO 25 mg/kg q6hr 2. Amphotericin B lipid complex 3-4 mg/kg/day + fluconazole^b 800 mg PO/IV daily 3. Liposomal amphotericin IV 3–4 mg/kg/day + fluconazole^b 800 mg PO/IV daily Preferred: Consolidation therapy x 8 wk Fluconazole^b PO/IV 400 mg/day Preferred: Maintenance therapy × 1 yr Fluconazole PO/IV 200 mg/day
Cytomegalovirus: Primary prophylaxis not indicated Secondary prophylaxis may be considered	Secondary prophylaxis: Valganciclovir^b PO 900 mg/day	Preferred: Induction: Valganciclovir^b PO 900 mg BID for 14–21 days *or* Ganciclovir^b 5 mg/kg q12hr for 14–21 days Alternatives: 1. Foscarnet^b IV 90 mg/kg q12hr or 60 mg/kg q8hr for 14-21 days 2. Cidofovir IV 5 mg/kg/wk for 2 doses (with probenecid 2 g 3 hr before cidofovir; then 1 g 2 hr after cidofovir and 1 g 8 hr after the dose)

[a] Should not be used in patients with a glucose-6-phosphate dehydrogenase deficiency

[b] Renal adjustments may be necessary.

[c] Monitor for interactions with HAART.

BID = twice daily; DS = double strength; hr = hour(s); INH = isoniazid; IV = intravenous(ly); OI = opportunistic infection; PO = orally; SS = single strength; TIW = thrice weekly; TMP/SMX = trimethoprim/sulfamethoxazole.

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Table 12. Common Interactions Between Antiretrovirals and Commonly Used Medications in Critically Ill Patients

Agent	Antiretroviral	Interactions
Stress ulcer prophylaxis (proton pump inhibitors, histamine-2 receptor antagonists)	Rilpivirine: Contraindicated with proton pump inhibitors Atazanavir: Relatively contraindicated with proton pump inhibitors (administer no more than the equivalent of omeprazole 20 mg daily, and separate administration by at least 12 hr)	Decrease in antiretroviral concentrations
Triazole antifungals: Voriconazole, posaconazole, itraconazole, isavuconazole	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Increase in antiretroviral concentration Decrease in antifungal concentrations
Antibacterials:		
Rifampin	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Decrease in antiretroviral concentration
Clarithromycin	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Increase in clarithromycin concentration
Metronidazole	Fosamprenavir, lopinavir, ritonavir	Disulfiram reaction
Antiarrhythmics:		
Amiodarone	Indinavir, ritonavir, tipranavir	Increased antiarrhythmic concentrations
Flecainide, propafenone, quinidine	Lopinavir, ritonavir, tipranavir	
Diltiazem	Atazanavir, fosamprenavir	
Statins	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Increase concentrations of statins – in decreasing order of interaction potential (lovastatin, simvastatin, rosuvastatin, atorvastatin, pravastatin)
Anticonvulsants: Carbamazepine, phenobarbital, phenytoin	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors	Decrease in antiretroviral concentrations Increase or decrease in anticonvulsant concentrations
Midazolam	Protease inhibitors Nonnucleoside reverse transcriptase inhibitors Cobicistat/elvitegravir	Increase in midazolam concentration
Methadone	Nonnucleoside reverse transcriptase inhibitors; fosamprenavir, ritonavir, lopinavir, nelfinavir, didanosine, saquinavir	Decrease in methadone concentration (potentially leading to opioid withdrawal)

Table 12. Common Interactions Between Antiretrovirals and Commonly Used Medications in Critically Ill Patients *(continued)*

Agent	Antiretroviral	Interactions
Sildenafil	Protease inhibitors; delavirdine	Increase in sildenafil concentration
Anticoagulants: Warfarin Apixaban Rivaroxaban	Delavirdine, efavirenz Protease inhibitor/cobicistat, protease inhibitor/ritonavir Protease inhibitor/cobicistat, protease inhibitor/ritonavir	Increase in warfarin concentration Increases in apixaban concentrations: Do not administer in patients who require 2.5 mg BID; in patients requiring 10 mg or 5 mg twice daily, reduce apixaban by 50% Increases in rivaroxaban expected: Do not coadminister

IX. ANTIFUNGAL THERAPY

A. Amphotericin B
   1. Mechanism of action: Binds to ergosterol in the fungal cell membrane, which alters the membrane permeability, leading to ion leakage and fungal cell death
   2. Spectrum of activity
      a. *Candida* spp. (except for *C. lusitaniae*), Blastomycetes, coccidioidomycosis, *Cryptococcus*, *Paracoccidioides*, histoplasmosis, aspergillosis, mucormycosis
      b. Wide spectrum of activity allows its clinical use in many different systemic fungal infections.
   3. Dose
      a. Conventional amphotericin: 0.5–1.0 mg/kg/day
      b. Lipid amphotericin: 3–5 mg/kg/day (higher doses have not been associated with improved outcomes)
   4. Adverse effects
      a. Renal toxicity
         i. Decrease in glomerular filtration rate, which is associated with cumulative doses greater than 4–5 g
         ii. Clinical manifestation
            (a) Renal tubular acidosis
            (b) Oliguria
            (c) Azotemia
            (d) Potassium, magnesium, phosphate wasting
         iii. Prevention
            (a) Avoid concomitant nephrotoxins.
            (b) Avoid dehydration.
            (c) Salt loading: 500 mL of normal saline before and after infusion of amphotericin
      b. Infusion-related reactions
         i. Mediated by cytokine release and prostaglandin synthesis
         ii. Presentation: Fever, chills, nausea, vomiting, flushing, rigors
         iii. Prevention
            (a) Premedications – Administered 30–60 minutes before infusion
               (1) Hydrocortisone 25–50 mg intravenously/orally

(2) Ibuprofen 600 mg orally

(3) Acetaminophen 650 mg orally with diphenhydramine 50 mg orally

(4) Meperidine 25–50 mg intravenously if patient previously experienced rigors

(b) Use lower infusion rate on dose initiation.

c. Lipid amphotericin (liposomal amphotericin and amphotericin B lipid complex)

i. Amphotericin dissociates from lipid over time, which may limit its renal toxicity and infusion-related reactions.

ii. Premedication may still be necessary for amphotericin B lipid complex.

B. Triazole Antifungals

1. Mechanism of action: Inhibits the synthesis of ergosterol through blocking the CYP enzyme 14-α-sterol-demethylase. Inhibition of this enzyme leads to the accumulation of 14-α-methyl sterols on the fungal surface, which in turn leads to fungal cell death.

2. Fluconazole

a. Spectrum of activity:

i. *Candida* spp.

(a) *Candida krusei* is intrinsically resistant.

(b) Variable sensitivity with *Candida glabrata*. Should not be used for *C. glabrata* unless antifungal susceptibilities are available. If *C. glabrata* is sensitive dose-dependent, higher doses may be necessary (12 mg/kg/day).

(c) Good activity against all other pathogenic *Candida* spp.

ii. *Cryptococcus*

b. Dose

i. 6–12 mg/kg/day (400–800 mg/day)

ii. Available in intravenous and oral formulations

iii. Well absorbed orally with high bioavailability

iv. Primarily excreted by the kidneys – Renal dose adjustments are necessary.

c. Adverse effects: Minimal adverse effects and lowest propensity for drug interactions among triazoles

3. Itraconazole

a. Spectrum of activity

i. *Candida* spp. – Has coverage similar to fluconazole with the addition of activity against *C. krusei*

ii. *Aspergillus*, *Blastomyces*, *Histoplasma*

b. Dose

i. 200–400 mg once daily

ii. Intravenous formulation no longer available

iii. Poor and erratic oral absorption. Improved with oral liquid formulation, maintaining high stomach acidity, avoidance of acid-suppressive therapy, and coadministration with acidic beverage

iv. Therapeutic drug monitoring may be necessary. Please see the Pharmacokinetics/Pharmacodynamics chapter for further discussion.

v. Primarily used for fungal prophylaxis in immunocompromised patients and treatment of endemic fungi (histoplasmosis, blastomycosis)

c. Adverse effects

i. GI upset, increase in liver function tests

ii. Drug interactions: CYP 3A4 and 2C9 inhibitor

4. Voriconazole
   a. Spectrum of activity
      i. *Candida* spp. – Has coverage similar to fluconazole with the addition of activity against *C. krusei*
      ii. *Aspergillus*, *Fusarium*, *Scedosporium*: Resistance against voriconazole has occurred with these pathogens.
   b. Dose
      i. Drug of choice for invasive aspergillosis
      ii. 6 mg/kg every 12 hours x 2 doses as the loading dose, followed by 4 mg/kg every 12 hours
      iii. Intravenous and oral formulations are available.
      iv. Intravenously formulated in sulfobutyl-ether-β-cyclodextrin, which accumulates in renal dysfunction, although the clinical significance of this is unknown
      v. Extensively metabolized by the liver, with 50% dose reductions recommended for patients with moderate to severe cirrhosis
      vi. Genetic variations in CYP metabolism and high propensity for drug interactions lead to wide interpatient variability in concentrations.
      vii. Therapeutic drug monitoring may be necessary. Please see the Pharmacokinetics/Pharmacodynamics chapter for a discussion on voriconazole therapeutic drug monitoring.
   c. Adverse reactions
      i. Increase in liver function tests
      ii. Visual hallucinations
      iii. Rash
      iv. Nausea
      v. CYP 3A4 and 2C9 inhibitor:
         (a) Contraindicated with the use of rifampin, rifabutin, sirolimus, barbiturates, carbamazepine, and quinidine
         (b) Significant dose reductions for cyclosporine and tacrolimus when coadministered with voriconazole
      vi. QTc prolongation
5. Posaconazole
   a. Spectrum of activity: Wide spectrum of activity, which includes *Candida* (similar to voriconazole), *Aspergillus*, *Zygomycetes*, and *Fusarium*
   b. Dose
      i. Oral suspension (immediate release): 200 mg every 6 hours. Oral suspension has extremely erratic absorption that is enhanced by coadministration with a high-fat meal and acidic food. In critically ill patients in whom coadministration with fatty meals is not possible and avoidance of acid-suppressive stress ulcer prophylaxis cannot be avoided, would recommend considering an alternative therapy or administration method (e.g., oral tablets or intravenous)
      ii. Oral tablets (delayed release): 300 mg every 12 hours x 2 doses, followed by 300 mg once daily. Oral tablet is in an extended-release formulation, which cannot be crushed. Oral tablet absorption not as dependent on gastric pH and meal lipid content.
      iii. Intravenous: 300 mg every 12 hours x 2 doses, followed by 300 mg once daily (intravenously formulated in sulfobutyl-ether-β-cyclodextrin, which accumulates in renal dysfunction, although the clinical significance of this is unknown)
      iv. Therapeutic drug monitoring may be necessary. Please see the Pharmacokinetics/Pharmacodynamics chapter for further discussion.
      v. Mainly used for fungal prophylaxis in immunocompromised patients and treatment when patient is not responding to other therapies

- c. Adverse reactions
    - i. Increase in liver function tests
    - ii. Nausea/vomiting
    - iii. Drug interaction: CYP3A4 inhibitor
    - iv. QTc prolongation
6. Isavuconazole
    - a. Spectrum of activity: Wide spectrum of activity, including *Candida* (similar to voriconazole), *Aspergillus* (may retain activity for some species that are resistant to other azoles), *Zygomycetes*, and dimorphic fungi. Limited activity against *Fusarium*.
    - b. Dose
        - i. Isavuconazonium: Loading dose 372 mg (equivalent to 200 mg of isavuconazole) every 8 hours intravenously × 6 doses, maintenance dose 372 mg (equivalent to 200 mg of isavuconazole) daily
        - ii. Isavuconazonium sulfate solution is readily water soluble, unlike posaconazole and voriconazole, and does not require stabilization with cyclodextrin.
    - c. Mainly PK advantages and safety benefits over voriconazole and posaconazole
        - i. Linear kinetics
        - ii. Oral bioavailability: 98%, not affected by food or acidity
        - iii. Fewer drug-drug interactions
        - iv. No QTc prolongation; in fact, associated with dose-dependent QTc shortening

C. Echinocandins (caspofungin, micafungin, rezafungin, and anidulafungin)

1. Mechanism of action: Inhibition of glucan synthase, which is an enzyme responsible for the formation of 1,3-β-d-glucan. Inhibition of this enzyme leads to cessation of fungal cell wall formation.
2. Spectrum of activity: All *Candida* spp. and *Aspergillus*
    - a. In vitro, *C. parapsilosis* has a much higher MIC than other *Candida* spp. The clinical significance of this is unknown. Cases of breakthrough infections with *C. parapsilosis* during treatment with echinocandins have been reported. Several retrospective studies did not find worsened outcomes associated with echinocandin treatment of *C. parapsilosis*. The current IDSA guidelines on invasive candidiasis recommend using fluconazole for the treatment of *C. parapsilosis*.
    - b. Primarily used for invasive candidiasis, neutropenic fever, and invasive *Aspergillus* if patient cannot tolerate other therapies. Recent IDSA candidiasis guidelines recommend echinocandin as preferred initial therapy for both proven and empiric therapy.
3. Dose (available only as an intravenous formulation)
    - a. Caspofungin: 70 mg once, followed by 50 mg once daily
    - b. Micafungin: 100 mg once daily
    - c. Anidulafungin: 200 mg once, followed by 100 mg once daily
    - d. Rezafungin 400 mg intravenously once on day 1, followed by 200 mg intravenously weekly beginning on day 8 for up to four doses
4. Adverse reactions
    - a. Well tolerated with minimal GI adverse effects
    - b. Minimal drug interactions
        - i. Avoid caspofungin coadministration with cyclosporine and tacrolimus.
        - ii. Avoid micafungin coadministration with nifedipine and sirolimus.
        - iii. Avoid administering anidulafungin with metronidazole (disulfiram reaction).

5. Empiric treatment of critically ill patients: A recent large, multicenter study evaluated the use of empiric micafungin in immunocompromised critically ill patients with sepsis, multiple *Candida* colonization, multiorgan failure, and exposure to broad-spectrum antibiotics. The study showed no improvement in fungal infection-free survival compared with placebo. Until further evidence is available, empiric echinocandins should not be administered routinely.

D. Flucytosine
  1. Mechanism of action: Converted by fungal enzymes to fluorouracil, which disrupts fungal RNA and DNA synthesis
  2. Spectrum of activity
    a. *Candida* spp.
    b. *Cryptococcus*: Treatment of choice (in conjunction with amphotericin) for C*ryptococcus* meningitis
  3. Dose
    a. 25 mg/kg every 6 hours
    b. Renal adjustments necessary
    c. Well absorbed: Bioavailability 80%–90%
    d. Available only as an oral formulation in the United States
    e. Therapeutic drug monitoring may be necessary. Please see the Pharmacokinetics/Pharmacodynamics chapter for further discussion.
  4. Adverse reactions: Bone marrow suppression, particularly with supratherapeutic concentrations

Patient Case

8. A 66-year-old woman (height 66 inches, weight 75 kg) is admitted to the medical ICU for dehydration and acute kidney injury. The patient recently received an allogeneic bone marrow transplant and has not yet engrafted. She has been pancytopenic for 12 days. On day 5 of the medical ICU stay, the patient develops acute respiratory distress requiring intubation. Bronchoalveolar lavage is done, which eventually grows *Aspergillus fumigatus*, and the patient is given a diagnosis of invasive pulmonary aspergillosis. The patient's current medications include tacrolimus, corticosteroids, and fluconazole fungal prophylaxis. Her current relevant laboratory values are as follows: WBC 0.2 x 10^3 cells/mm^3, lactate 1.5 mmol/L, and SCr 3.4 mg/dL. Which antifungal therapy is most appropriate?
  A. Amphotericin 50 mg intravenously once daily.
  B. Isavuconazole load followed by 200 mg intravenously daily.
  C. Caspofungin load followed by 50 mg intravenously daily.
  D. Voriconazole load followed by 300 mg intravenously every 12 hours.

X. SOCIAL DETERMINANTS OF HEALTH AND INFECTIOUS DISEASES

A. Social determinants of health are categorized by the CDC into the following domains:
  1. Healthcare access and quality
  2. Economic stability
  3. Neighborhood and built environment
  4. Education access and quality
  5. Community and social context

B. Social determinants of health are a key focus of Healthy People 2030: "Create social, physical, and economic environments that promote attaining the full potential for health and well-being for all."

C. The WHO has put forth a conceptual framework for acting on social determinants of health to reduce health inequities and improve overall health and well-being.

D. Research has connected several social determinants of health factors with the following:
  1. Vaccination
  2. HIV
  3. Viral hepatitis
  4. Sexually transmitted diseases
  5. Tuberculosis
  6. COVID-19
     a. Many social determinants of health including poverty, physical environment, and race or ethnicity can have a considerable effect on COVID 19 outcomes.

E. Often people in poverty have limited access to health care, must work when they are sick, and face more stress, which can impact immunity and increase susceptibility to infection and death.

F. By remaining intentional about decreasing unconscious biases and seeing past medications to the individual to identify potential barriers, pharmacists can bolster the movement toward health equity.

G. The Pharmacy Quality Alliance issued a resource guide to help pharmacists navigate social determinants of health (https://www.pqaalliance.org/sdoh-resource-guide).

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

The CDC definitions for CAUTIs, which are used by the CMS reporting system, were recently updated. Because this patient had his urinary catheter removed for more than 24 hours before developing UTI symptoms, this case does not satisfy the definition of CAUTI (Answer D is correct; Answers A and C are incorrect). The current CDC CAUTI definitions do not consider the results of a urinalysis (Answer B is incorrect).

2. **Answer: A**

This patient presents with community-acquired meningitis. The high opening pressure is suggestive of a bacterial etiology, of which the most prevalent pathogen for this patient's risk factors and age is *S. pneumoniae*. Administering dexamethasone before initiating antibiotic therapy decreases mortality in patients with *S. pneumoniae* meningitis. (Answer A is correct) Awaiting laboratory and microbiologic test results analysis may cause inappropriate delays in therapy (Answer B is incorrect). In addition, although administering antimicrobials is a good idea, the beneficial effects associated with dexamethasone are diminished if administered after antimicrobials have been initiated. At the very least, corticosteroids should be administered concomitantly with antimicrobials (Answer C and D are incorrect).

3. **Answer: D**

The PNA FISH technology is designed to identify pathogens earlier. It performs well, with good sensitivity and specificity; hence, identification of *C. parapsilosis* should not require verification from culture (Answer A is incorrect). The drug of choice for the treatment of *C. parapsilosis* is fluconazole (Answer D is correct). Although echinocandin, voriconazole, and amphotericin would all cover *C. parapsilosis,* they all have a broader spectrum than is necessary, making them not the ideal choice (Answers A–C are incorrect).

4. **Answer: A**

Although PCT is a promising biomarker for the detection of bacterial infections, it must be interpreted within the context of the patient's clinical course. In this case, the patient has clear signs and symptoms of infection, together with signs of hypoperfusion. A low PCT should not be used to guide therapy discontinuation in this case, and antibiotics should be continued to cover the most likely pathogens (Answer A is correct; Answer B is incorrect). Because the patient is admitted with presumed community-acquired pneumonia, the combination of ceftriaxone and azithromycin is appropriate right now (Answers C and D are incorrect).

5. **Answer: B**

This patient is being treated for an ESBL *E. coli* UTI, in which the source of the infection (urinary catheter) is removed. The patient also has signs of response to piperacillin/tazobactam with resolution of leukocytosis and fever. In this case, given the low inoculum of the infection, initial response, removal of source, and low MIC, continuing piperacillin/tazobactam is the best choice (Answer B is correct). This choice may only be the case for UTIs, not other sources of infection (e.g., bacteremias). Traditionally, it was widely believed that ESBL infections had to be treated with carbapenems. However, recent evidence suggests that β-lactam/β-lactamase inhibitor combinations are a suitable option. In the era of antimicrobial stewardship, the preservation of carbapenem therapy should be regarded with high importance (Answer A is incorrect). This current culture has an MIC of 4 mcg/mL to cefepime, which, according to the updated CLSI guidelines, would be considered resistant (Answer C is incorrect). Because the patient is responding to the current therapy, combination therapy is unnecessary (Answer D is incorrect).

6. **Answer: D**

This patient is being treated for MRSA right-sided endocarditis, with the presumed source from her tunneled dialysis catheter. According to the IDSA guidelines for the treatment of MRSA, treatment with vancomycin of an isolate with an MIC of 2 mcg/mL or less should be determined by the patient's response to therapy, regardless of the actual MIC. This patient has responded to therapy with the presumed clearance of blood cultures and resolution of signs and symptoms of infection. Hence, continuing vancomycin and targeting a trough of 15–20 mcg/mL is the most appropriate choice (Answer D is correct). Linezolid is not indicated for the treatment of endocarditis (Answer A is incorrect). Adding gentamicin and rifampin is considered in the medical treatment of prosthetic valve endocarditis (Answer B is incorrect). Because the patient is responding to current vancomycin therapy, an escalation to daptomycin is inappropriate right now (Answer C is incorrect).

7. **Answer: B**

This patient is admitted to the ICU for an indication that is unrelated to the patient's underlying HIV. The assessment of which prophylactics are necessary against OIs depends on the patient's underlying disease, history, and $CD4^+$ count. In this case, the patient has a $CD4^+$ count less than $100/mm^3$ and a history of cryptococcal meningitis. Hence, prophylaxis should be administered for toxoplasmosis, *P. jiroveci*, and *Cryptococcus*. The best regimen for this patient is fluconazole 200 mg daily and trimethoprim/sulfamethoxazole 1 DS tablet once daily (Answer B is correct). The prophylaxis for *M avium* complex is indicated for patients with a $CD4^+$ count of less than 50 cells/mm^3, which is unnecessary at this point (Answers A and C are incorrect). Although trimethoprim/sulfamethoxazole 1 DS tablet thrice weekly is an option for prophylaxis, it is not the best choice against toxoplasmosis (Answer D is incorrect).

8. **Answer: B**

This patient has invasive pulmonary aspergillosis. Usually, the treatment of choice is voriconazole. However, in this case, the patient has acute kidney injury with a CrCl less than 50 mL/minute/1.73 m^2. According to the package insert, voriconazole is contraindicated in this case because of the possibility of accumulation of cyclodextrin, the intravenous drug carrier for voriconazole. Although the clinical relevance of this accumulation is controversial, continued use of a contraindicated therapy is inappropriate when alternatives may be available (Answer D is incorrect). Isavuconazole is a new triazole that was found to be noninferior to voriconazole for the treatment of aspergillosis and has improved water solubility, which does not require it to be formulated with cyclodextrin (Answer B is correct). Conventional amphotericin may be a reasonable choice, but it will likely worsen the patient's acute kidney injury (Answer A is incorrect). Echinocandins are not the ideal therapies for invasive aspergillosis and should only be considered if there are no other treatment options. In addition, caspofungin can decrease the serum concentration of tacrolimus (Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

The prophylactic regimen for a patient without a β-lactam allergy who is undergoing cardiac surgery should be cephalosporin administered within 60 minutes of incision time, administered every 4 hours during surgery, and continued for no more than 48 hours. In this case, the patient has obesity disorder and weighs more than 120 kg; hence, the patient requires an initial dose of cefazolin 3 g (Answer C is correct). Given the patient's weight, administering cefazolin 2 g initially is inappropriate (Answers A and D are incorrect). Vancomycin is usually reserved for patients with a β-lactam allergy (Answer B is incorrect).

2. **Answer: C**

Although critical care pharmacists may not officially be part of many antimicrobial stewardship teams, many of their daily clinical activities constitute antimicrobial stewardship activities. These may include selecting the most appropriate treatment regimen and advocating the early de-escalation of antimicrobials. Even in the presence of a formalized antimicrobial stewardship team, these activities are often complementary to the formalized activities of the team (Answer C is correct). Given the wide variations in clinical practice, it may not be feasible to include an infectious diseases–trained pharmacist with every stewardship team. In that case, the activities and involvement of a critical care pharmacist may be even more crucial (Answer A is incorrect). Antimicrobial cycling has not consistently demonstrated beneficial effect on antimicrobial resistance. (Answer B is incorrect). Studies have shown that antimicrobial stewardship efforts in critically ill patients do not worsen outcomes. Given the aggressive empiric antimicrobial regimens commonly used in critically ill patients, antimicrobial stewardship should be instituted to minimize adverse effects and the emergence of resistance (Answer D is incorrect).

3. **Answer: D**

This patient presents with a health care–associated CNS infection, given the post-neurosurgical and device-related etiology of the infection. The most common pathogens include MRSA and multidrug-resistant gram-negative organisms. In addition to neurosurgical management of the device (e.g., removal or revision), empiric antibiotic therapy is indicated, including therapy with agents having empiric activity against suspected pathogens and the ability to safely achieve relevant CSF concentrations. Cefepime and vancomycin are the most appropriate options listed with consideration of CNS-specific dosing (Answer D is correct). Ceftriaxone does not cover nosocomial-acquired gram negatives such as *Pseudomonas* (Answers A and B are incorrect). Piperacillin/tazobactam would be reasonable according to the spectrum of antibacterial activity; however, poor CNS penetration of tazobactam limits the utility of this agent for meningitis and other CNS infections (Answer C is incorrect).

4. **Answer: D**

The presence of the CTX-M gene detected on *E. coli* by rapid diagnostic testing usually signifies the presence of ESBL. This may be why the patient has not yet responded to piperacillin/tazobactam. The most appropriate action at this point is to broaden the coverage to cover for potential ESBL-producing *E. coli*. Carbapenems remain the drug of choice for ESBL-producing organisms, particularly in a patient who is hemodynamically unstable (Answer D is correct). Extended-spectrum β-lactamases are usually encoded on genes that carry resistance against other classes of antimicrobials; hence, resistance to other antimicrobials is common; therefore, adding either aminoglycosides or fluoroquinolones may not be appropriate (Answers B and C are incorrect). Although at times ESBLs may be covered by cefepime, it must be determined by final AST (Answer A is incorrect).

5. **Answer: C**

E. cloacae are AmpC β-lactamase–producing Enterobacterales. The use of ceftriaxone or extended-spectrum penicillins (e.g., piperacillin and ticarcillin) may select out derepressed mutants, which are capable of causing the hyperproduction of AmpC β-lactamases. Derepressed mutants are capable of producing resistance against third-generation cephalosporins, monobactams, and extended-spectrum penicillins. In this case, the patient was taking 10 days of ceftriaxone before a new blood culture was growing lactose-positive gram-negative bacilli. Because lactose-positive gram-negative bacilli are usually Enterobacterales, growing multidrug-resistant pathogens such as *P. aeruginosa* and *Acinetobacter baumannii* is less likely. Hence, the most likely resistance mechanism in this patient is either selection of derepressed mutants or acquisition of a pathogen with ESBL. Both of these resistance mechanisms are adequately treated by a carbapenem. Hence, changing to a carbapenem pending final sensitivities is the most reasonable option (Answer C is correct). Both types of resistance mechanisms are capable of producing resistance against ceftazidime and piperacillin/tazobactam (Answers A and B are incorrect). Because the patient developed a new bacteremia while taking ceftriaxone, it is not reasonable to continue ceftriaxone alone (Answer D is incorrect).

6. **Answer: B**

The patient is only on day 4 of therapy from proven MRSA pneumonia. However, the patient developed a bacteremia with gram-positive cocci in pairs and chains despite receiving systemic vancomycin therapy. The most likely culprit is a vancomycin-resistant *Enterococcus* sp. The medical team has already discontinued vancomycin; therefore, the new therapy must cover both the MRSA pneumonia and the possibility of a vancomycin-resistant *Enterococcus* sp. Linezolid has good lung penetration and can adequately cover vancomycin-resistant enterococci (Answer B is correct). Daptomycin would provide adequate coverage for vancomycin-resistant enterococci, but because it is inactivated by lung surfactants, it is not a good option for the treatment of MRSA pneumonia (Answer A is incorrect). Ceftaroline covers MRSA and has good lung penetration; however, it covers only vancomycin-resistant *E. faecalis*, not *E. faecium*. Because, at this point, the speciation of the gram-positive cocci in pairs and chains is not available, ceftaroline is not the best choice (Answer C is incorrect). Tigecycline does cover MRSA and vancomycin-resistant enterococci; however, given its large volume of distribution and relatively low serum concentrations, it is not the ideal choice for the treatment of bacteremia when other treatments are available (Answer D is incorrect).

7. **Answer: B**

The patient's history and clinical presentation suggest *Pneumocystis jiroveci* pneumonia. It is severe enough to warrant intubation, and the patient has a significant alveolar-arterial oxygen gradient. The usual drug of choice for such patients is trimethoprim/sulfamethoxazole, but because this patient has a sulfa allergy, this is not an option (Answer A is incorrect). According to the HIV OI guideline, the second-line agent for the treatment of severe *Pneumocystis jiroveci* pneumonia is intravenous pentamidine. Because the patient had severe hypoxemia, adjunctive steroids should be administered (Answer B is correct). Atovaquone and primaquine/clindamycin regimens are usually reserved for patients with milder *Pneumocystis jiroveci* pneumonia. Furthermore, primaquine should not be administered to someone with a glucose-6-phosphate dehydrogenase deficiency (Answers C and D are incorrect).

8. **Answer: B**

This patient has febrile neutropenia with no recovery of neutrophils. According to the IDSA febrile neutropenia guidelines, when a source of infection is identified, the empiric antimicrobial therapy can be de-escalated to a more narrow-spectrum regimen according to the antibiotic susceptibility report. In this case, because the *E. coli* was pan-sensitive, it would be appropriate to de-escalate to a narrow-spectrum antimicrobial. The guidelines also specify that antimicrobial therapies should be continued for at least 14 days and until neutrophils are greater than 500 cells/mm^3 (Answer B is correct). Although the patient continues to be febrile, an otherwise stable patient with continued fevers rarely requires additional antimicrobial therapy according to the guidelines. Hence, continuing more broad-spectrum therapy than necessary or adding other antimicrobials is unwarranted (Answers A, C, and D are incorrect).

PHARMACOKINETICS/ PHARMACODYNAMICS

JOSEPH M. SWANSON, PHARM.D., FCCP, FCCM

UNIVERSITY OF TENNESSEE COLLEGE OF PHARMACY
MEMPHIS, TENNESSEE

CHRISTOPHER A. DROEGE, PHARM.D., FCCP, FCCM, FASHP

UC HEALTH - UNIVERSITY OF CINCINNATI MEDICAL CENTER
CINCINNATI, OHIO

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Learning Objectives

1. Describe the changes in critically ill patients that alter drug absorption.
2. Explain how critical illness affects drug distribution.
3. Depict the effects of changing hepatic blood flow, intrinsic activity, and protein binding on drug metabolism.
4. Differentiate between different critically ill patient populations and the expected pharmacokinetic (PK) changes.
5. Identify the desired pharmacodynamic variables associated with efficacy in select drugs.

Abbreviations in This Chapter

AAG	α_1-Acid glycoprotein
AKI	Acute kidney injury
ARC	Augmented renal clearance
AUC	Area under the curve
AUC/MIC	Ratio of area under the curve to the minimum inhibitory concentration for the bacterial pathogen
AUC_{0-24}/MIC	Ratio of area under the curve for 24 hours to the minimum inhibitory concentration for the bacterial pathogen
CKD	Chronic kidney disease
$C_{max/MIC}$	Ratio between the maximum drug concentration and the minimum inhibitory concentration for the bacterial pathogen
fT>MIC	Free drug concentration time above the minimum inhibitory concentration for the bacterial pathogen
ECMO	Extracorporeal membrane oxygenation
GFR	Glomerular filtration rate
ICU	Intensive care unit
MIC	Minimum inhibitory concentration
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
TBI	Traumatic brain injury
TDM	Therapeutic drug monitoring
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. J.H. is a 30-year-old man admitted to the intensive care unit (ICU) for septic shock. He initially received 30 mL/kg of normal saline for intravenous fluid resuscitation. He required further fluid administration to improve his pulse pressure variation. Despite prophylaxis with enoxaparin 30 mg subcutaneously every 12 hours, J.H. has a proximal deep venous thrombosis. Which pharmacokinetic (PK) alteration most likely contributed to this therapeutic failure?
    A. Decreased anti-factor Xa (anti-Xa) activity secondary to decreased volume of distribution (Vd).
    B. Decreased anti-Xa activity secondary to decreased absorption.
    C. Increased anti-Xa activity secondary to decreased hepatic metabolism.
    D. Increased anti-Xa activity secondary to decreased renal elimination.

Questions 2–4 pertain to the following case.

E.W. is a 48-year-old man (height 70 inches, weight 85 kg) admitted to the trauma ICU after a motorcycle collision. E.W. presents with a traumatic brain injury (TBI; head computed tomography [CT] reveals a depressed skull fracture, frontal subarachnoid hemorrhage, and right intraparenchymal hemorrhage), right acetabulum fracture, bilateral rib fractures, and abdominal trauma. According to his abdominal CT, E.W. must go to the operating room for an exploratory laparotomy for repair of several serosal tears. After surgery, E.W. requires significant resuscitation in his first 24 hours of admission (5 L of normal saline). He is made NPO to allow bowel rest.

E.W.'s laboratory values are as follows: serum creatinine (SCr) 1.1 mg/dL, blood urea nitrogen (BUN) 17 mg/dL, and white blood cell count (WBC) 19 × 10^3 cells/mm^3. The patient's pulmonary artery catheterization values are cardiac index 4.2 L/minute/m^2 (normal 2.8–3.6 L/minute/m^2) and pulmonary artery wedge pressure 16 mm Hg. His medication therapy includes a fentanyl continuous infusion of 75 mcg/hour, a propofol continuous infusion of 15 mcg/kg/minute, pantoprazole 40 mg intravenously every 24 hours, enoxaparin 30 mg subcutaneously every 12 hours, and fosphenytoin 150 mg intravenously every 8 hours.

2. Which most accurately assesses the risk factors for the decreased absorption of enterally administered drugs?
   A. Intestinal atrophy, pantoprazole therapy, abdominal surgery.
   B. TBI, fentanyl therapy, cardiac output.
   C. Abdominal surgery, pantoprazole therapy, TBI.
   D. Intestinal atrophy, cardiac output, fentanyl therapy.

3. Before E.W.'s ICU admission, his albumin concentration was 3.8 g/dL, but after surgery, it decreased to 2.1 g/dL. Given this change in albumin, which change in the total and unbound concentration of propofol would be most likely?
   A. Increased total concentration, decreased unbound concentration.
   B. No change in total concentration, increased unbound concentration.
   C. Increased total concentration, no change in unbound concentration.
   D. Decreased total concentration, increased unbound concentration.

4. On postoperative day 3, E.W.'s SCr increased to 3 mg/dL. On postoperative day 4, his SCr is 3.2 mg/dL. Which variable for assessing kidney function would be most important for determining E.W.'s dosing adjustments?
   A. BUN/SCr ratio.
   B. Total daily urinary output.
   C. Estimation of glomerular filtration rate (GFR).
   D. History of chronic kidney disease (CKD).

Questions 5 and 6 pertain to the following case.
S.H. is a 35-year-old man (height 70 inches, weight 85 kg) admitted to the medical ICU because of sepsis caused by hospital-acquired pneumonia. He is empirically treated with intermittent vancomycin, piperacillin/tazobactam, and ciprofloxacin. His laboratory values are as follows: SCr 1 mg/dL, BUN 12 mg/dL, and WBC 18×10^3 cells/mm^3.

5. According to S.H.'s anticipated PK changes and guideline recommendations, which would be the most appropriate intravenous loading dose of vancomycin?
   A. 1000 mg.
   B. 1500 mg.
   C. 2500 mg.
   D. 3500 mg.

6. S.H. is given a diagnosis of methicillin-resistant *Staphylococcus aureus* hospital-acquired pneumonia. On day 10 of vancomycin therapy, his vancomycin area under the curve (AUC) is 700 mg x h/L. His previous vancomycin AUC was 425 mg x h/L on the same dosing regimen. Which most likely explains what transpired?
   A. Augmented renal excretion returned to normal.
   B. Vd increased to larger than normal.
   C. Tissue penetration decreased to below normal.
   D. Liver blood flow returned to normal.

7. B.B. is 40-year-old woman with a surgical site infection caused by *Pseudomonas aeruginosa*. She is initiated on a piperacillin/tazobactam 3.375 g intravenous infusion over 4 hours every 8 hours. Which is the most likely benefit of this approach with piperacillin/tazobactam?
   A. Decreased mortality supported by prospective controlled studies.
   B. Decreased neurotoxicity supported by prospective controlled studies.
   C. Decreased mortality supported by retrospective reviews.
   D. Decreased neurotoxicity supported by retrospective reviews.

8. C.W. is a 52-year-old man admitted to the ICU for acute respiratory failure. He is given scheduled oral morphine for pain control. Which PK variable would most likely affect the hepatic metabolism of morphine?
   A. Increased α_1-acid glycoprotein (AAG).
   B. Decreased albumin.
   C. Increased hepatic blood flow.
   D. Increased intrinsic clearance.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 2
    b. Task B: 2–5
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 2, 3, 6
    b. Task C: 1–4
3. Domain 3: Professional Practice
    a. Task B: 1

I. INTRODUCTION

Pharmacokinetics (PK) refers to the movement of a drug throughout the body, particularly absorption, distribution, metabolism, and excretion (ADME) of a drug, whereas pharmacodynamics (PD) addresses the biochemical and physiologic effects of a drug on the body. Physiologic changes in critically ill patients cause alterations that affect the PK and PD of drugs. Although few studies evaluate the effect of these changes, clinicians must consider the general principles when making drug dosing decisions in critically ill patients. The most important consideration in critically ill patients is that changes can occur rapidly and with high frequency. A patient may have an altered PK variable on one day, only to experience changes that alter that variable in a completely different way on the following day. An example is a critically ill patient with augmented renal clearance (ARC) who then develops an acute kidney injury (AKI). The patient may have increased renal elimination of a specific drug, followed by decreased elimination when AKI occurs. Therefore, the critical care pharmacist should know how the principles can be altered and continually anticipate changes during a patient's stay in the ICU.

II. ROUTES OF ADMINISTRATION

A. Intravenous
   1. The intravenous route is the most widely used method of drug administration in the critically ill population. The bioavailability of an intravenously administered drug is 100%, thus ensuring the entire dose reaches the systemic circulation. As such, this route is preferred over other routes subject to reduced absorption.
   2. Although intravenous drug administration is the most popular method used in the ICU, it still poses several potential problems. The intravenous route does not guarantee penetration of the drug into sites outside the circulatory system. Examples of this include poor penetration of hydrophilic drugs into various tissues such as the meninges, pulmonary tissue, and bone. In conditions such as septic shock, drug penetration into muscle and subcutaneous tissue is lower than expected. Finally, there are reports documenting the severe adverse effects of inadvertent extravascular administration of a drug. There are several reports of drug (vesicants or non-vesicants, which can be cytotoxic or noncytotoxic) extravasation, which highlights this potential complication of intravenous administration. For example, extravasation of norepinephrine creates local vasoconstriction and tissue necrosis, which is sometimes severe enough to cause loss of a limb.

B. Enteral/Oral – Using the enteral or oral route of administration in critically ill patients results in variable drug bioavailability. The predominant concern for this route of administration in critically ill patients pertains to alterations in drug absorption. The issues pertaining to altered drug absorption are discussed in the next section. Of note, not all drugs show reduced absorption when administered enterally/orally to critically ill patients. One example comes from a study investigating the PK of atorvastatin, administered enterally. Compared with healthy volunteers, patients in the ICU had a significantly higher area under the curve (AUC) (110.5 ng/mL vs. 5.9 ng/mL, $p<0.01$) after a single dose of atorvastatin 20 mg. The increased AUC could only partly be explained by altered hepatic metabolism (Intensive Care Med 2009;35:717-21). A complicating factor with enteral administration is first-pass metabolism, which can significantly affect the bioavailability of hepatically metabolized drugs (discussed later in the chapter). As such, critical care clinicians should evaluate the use of the enteral/oral route because of both increased and decreased bioavailability with different enteral medications.

C. Subcutaneous/Intramuscular/Sublingual – Subcutaneous and intramuscular drug administration avoids first-pass metabolism by the liver and can increase the bioavailability of a drug. However, these routes still require the drug to be absorbed into the blood. Therefore, these routes are potentially affected by changes in absorption. Unlike with the enteral or oral route, clinicians do not routinely abandon the use of subcutaneously or intramuscularly administered medications. Examples include the continued use of low-molecular-weight heparins, insulin, and antipsychotics in patients with obesity for whom the absorption may be altered. In addition, clinicians should be aware of similar concerns for altered absorption in critically ill patients with sepsis or shock states because of changes in perfusion. Use of the sublingual route of administration in critically ill patients has not been thoroughly researched. However, one could expect that alterations in blood flow and absorption would cause similar concerns as for subcutaneous and intramuscular routes. Critical care clinicians should understand that the subcutaneous route may be used; however, little to no data are available in critically ill patients to determine if any pharmacokinetic changes will occur.

D. Inhalation – Administration of drugs directly into the lungs of critically ill patients is usually chosen to reduce systemic exposure and/or achieve a high concentration in the pulmonary tissue. The high local concentration is intended to maximize the therapeutic effect while reducing any adverse or unwanted effects. For example, the use of inhaled bronchodilators reduces unwanted systemic effects such as tachycardia. Antibiotics such as colistin and aminoglycosides are administered via inhalation to improve the antibiotic concentrations in the lungs and reduce exposure to the kidneys. Studies have demonstrated varying serum concentrations following inhaled administration of amikacin in critically ill patients, but these concentrations were much lower than when administered intravenously (J Antimicrob Chemotherapy 2016;71:3482-6). Additional research found that older age and higher positive end expiratory pressure (PEEP) independently predicted detectable serum tobramycin concentrations (Respir Care 2022;67:16-23). While inhaled antibiotics are used to reduce the likelihood of systemic adverse effects, the efficacy of this route of antibiotic administration is not well established. Drug particles of 1–5 micrometers have the best opportunity to be delivered to all areas of the lungs. Smaller particles will be exhaled without being deposited in the lower airways, whereas larger particles will be deposited in the large bronchi or the oropharynx. Several models of nebulizers are on the market that use different methods to achieve the desired particle sizes.

E. Intrathecal/Intraventricular – Use of the intraventricular route is intended to increase local concentrations and reduce systemic concentrations. Data evaluating the efficacy of this route of administration are lacking in the general population limited to case series. Despite the lack of data, clinicians use this route when treating multidrug-resistant meningitis with antibiotics, or for the administration of analgesics in patients with chronic pain.

Patient Case

1. M.J. is a 70-year-old man admitted to the neurosurgical ICU for an aneurysmal subarachnoid hemorrhage. His initial treatment included placement of an external ventricular drain. Subsequently, he had a maximum temperature of 101.5°F, a WBC of 15×10^3 cells/mm^3, and a cerebrospinal fluid culture positive for methicillin-resistant *S. aureus*. Intraventricular vancomycin 20 mg is used for therapy. Which is the best rationale for this approach?

   A. Demonstrated superiority to intravenous antibiotics.
   B. Maximizing localized antibiotic concentrations.
   C. Safer administration method.
   D. Reducing the ototoxicity of vancomycin.

III. ABSORPTION

A. Bioavailability (F) refers to the percentage of an administered dose of drug that reaches the systemic circulation. All non-intravenous medications are affected by absorption. Enterally administered medications are also affected through first-pass metabolism. Few studies directly assess the enteral absorption of drugs in critically ill patients, and the results vary. In addition, studies of enterally administered drugs do not differentiate whether plasma concentrations are altered because of changes in absorption or first-pass metabolism. Although data on absorption in critically ill patients are limited, clinicians must consider several factors if a route of administration other than intravenous is preferred.

B. Gastrointestinal (GI) Perfusion – Hypotension and/or shock are known to cause the shunting of blood toward the vital organs (e.g., brain, heart, lungs) and away from the less vital organs (e.g., muscles, skin, splanchnic organs), which can alter drug absorption.

1. GI absorption: No studies clearly show the effect of hypotension or shock on the oral or enteral absorption of drugs. Clinicians extrapolate changes in splanchnic blood flow to the likelihood that GI absorption is altered. Redistribution of blood away from the splanchnic circulation is thought to decrease drug absorption from the GI tract. The hyperdynamic phase of sepsis or septic shock can increase cardiac output, and studies have shown an increase in hepatosplanchnic (portal vein and hepatic artery) blood flow. In late-stage (decompensated) sepsis, it is thought that splanchnic blood flow is decreased, but no studies have verified this. This uncertainty in splanchnic blood flow and GI absorption leads many clinicians to forgo the enteral route for drug administration. One diagnostic test to consider to evaluate GI absorption is an oral acetaminophen test. Of note, one study evaluated the use of acetaminophen at a dose of 15 mg/kg with serum concentrations measured within 3 hours of administration. The majority of patients had detectable serum acetaminophen concentrations between 30 and 60 minutes with no adverse outcomes associated with its use, suggesting this intervention as a potential surrogate for GI absorption (Am J Ther 2023;30:e95-102).
2. Transdermal, subcutaneous, and intramuscular absorption: No studies have evaluated the effect of hypotension or shock on transdermal, subcutaneous, or intramuscular absorption. Similar to splanchnic circulation, the shunting of blood to vital organs reduces blood flow to the skin and muscles, which is thought to reduce absorption from these sites. This assumption is supported by the observation that critically injured trauma patients with edema have significantly lower anti-Xa and antithrombin activity after treatment with subcutaneous enoxaparin (Ann Surg 2023;277:734-1). Altered absorption is believed to be a contributing factor to these results. However, this may not be generalized to all critically ill patients because anti-Xa activity was not significantly different in edematous compared with nonedematous medical-surgical ICU patients after dalteparin administration (Crit Care 2006;10:R93). Furthermore, the direct effects of critical illness on coagulation may alter the pharmacodynamics of low molecular weight heparins and obscure the degree to which absorption impacts their effect.
3. Vasopressor effect: Vasopressors may contribute to regional hypoperfusion, which could result in decreased drug absorption. Vasopressin reduces splanchnic blood flow in patients with distributive shock. In septic shock, epinephrine results in reduced splanchnic blood flow. Dopamine is not as effective as norepinephrine in maintaining splanchnic blood flow in patients with stable distributive shock. Conversely, when gut perfusion is compared between cardiac surgery patients with and without vasodilatory shock, norepinephrine use results in higher intestinal perfusion. However, this is countered by a worse splanchnic oxygen demand versus supply. The variable effect of vasopressors on splanchnic perfusion creates enough concern that most clinicians abandon the use of orally or enterally administered drugs when vasopressors are being used. The large inter-individual pharmacokinetic variability seen with enterally administered fludrocortisone in patients with septic shock illustrate this concern. In addition, absorption from other sites could be impaired. One study investigated the anti-Xa

activity of the low-molecular-weight heparin certoparin in critically ill patients, of whom 40.3% were receiving vasopressors. Less than 50% of patients receiving standard doses of certoparin had anti-Xa activity in the antithrombotic range (0.1–0.3 IU/mL) (Crit Care 2005;9:R541-8).

C. Intestinal Atrophy – After 3–5 days of fasting, gut mucosal crypt depth and villus height can be decreased. This correlates with an abnormal lactulose-mannitol test, indicating increased gut permeability. Splanchnic hypoperfusion can further worsen gut hypoxia, exacerbating gut permeability. However, the effect of intestinal atrophy on drug absorption has not been systematically evaluated. Atrophy and the corresponding loss of integrity of the tight junctions could lead to an increased absorption of drugs that are absorbed through passive diffusion. Conversely, cellular dysfunction caused by atrophy might decrease the absorption of drugs that require active transport for absorption. Unfortunately, studies addressing the clinical significance of intestinal atrophy are difficult to conduct, thereby leaving a void in the current literature.

D. GI dysmotility – GI dysmotility has clearly been established in critically ill patients, with an incidence as high as 60%. Box 1 shows the factors in critically ill patients that are associated with delayed gastric emptying caused by dysmotility. Acetaminophen kinetics show that GI dysmotility causes a delay in absorption and a reduced peak concentration in most studies. Concern regarding PK changes in the presence of delayed gastric emptying is a major factor contributing to the avoidance of orally or enterally administered drugs in critically ill patients. GI dysmotility is usually treated using prokinetic agents such as metoclopramide or erythromycin. No data exist regarding the effect of prokinetics on drug absorption in critically ill patients with dysmotility. However, one study found that, in healthy individuals, coadministration of erythromycin and the controlled-release formulation of pregabalin resulted in a 17% decrease in AUC and a 13% decrease in peak plasma concentrations of pregabalin (Clin Drug Investig 2015;35:299-305). This suggests that prokinetics can affect the absorption of other medications. In the critically ill patient, the effect of prokinetics on the PK of orally or enterally administered remains unclear.

Box 1. Reasons for Delayed Gastric Emptying

Burns
Electrolyte abnormalities
GLP-1 agonists
Hyperglycemia
Ileus
Mechanical ventilation
Opioid analgesics
Postoperative ileus
Sepsis
Shock
Surgery
Trauma
Traumatic brain injury

E. Intestinal Drug Transporters – Transmembrane proteins such as P-glycoprotein (P-gp) and cytochrome P450 (CYP) enzymes play an integral role in drug absorption. In general, these transporters reduce the absorption of drug substrates. Therefore, decreased activity of these enzymes will theoretically increase the absorption of drugs that are substrates. Conversely, several intestinal transporters facilitate drug absorption and therefore decrease activity, which would decrease drug absorption. However, no PK studies evaluate changes in drug absorption caused by changes in intestinal transporters that are specifically related to critical illness or conditions often present in these patients. Increased proinflammatory cytokines in patients with conditions such as systemic inflammatory response syndrome and sepsis affect P-gp expression and activity. Therefore, enteral drug absorption can be altered in these states. However, no studies have directly investigated the effects of inflammatory states, or systemic inflammatory response syndrome, on drug absorption changes mediated by changes in P-gp activity.

F. Physical Incompatibilities – Drugs administered through enteral feeding tubes come in contact with gastric secretions, intestinal secretions, and enteral nutrition formulas, all of which may pose a problem for drug absorption.

1. Drug-enteral-nutrition interactions: Some drugs potentially interact with enteral nutrition. The degree of interaction and clinical significance varies.
    a. Ciprofloxacin bioavailability is reduced when it is administered with enteral nutrition (with the exception of the oral suspension), but most studies suggest that serum concentrations remain above the minimum inhibitory concentration (MIC) for most bacterial pathogens.
    b. Enteral nutrition has been reported to significantly reduce the absorption of levothyroxine, phenytoin, and warfarin. One case report showed a reduction in voriconazole serum concentrations when enteral nutrition was initiated (J Oncol Pharm Pract 2012;18:128-31).
    c. A suggested solution to this interaction is to hold the enteral nutrition 1–2 hours before and after drug administration. However, this poses two problems. First, interruption of enteral nutrition may contribute to inadequate nutrition support. Second, this increases the difficulty of administering the medications appropriately. Increasing the workload of nurses can lead to administration delays or, even worse, errors. This is very important, because failure to withhold the enteral nutrition could result in suboptimal dosing and effects of the interacting drug.
2. pH changes: The state of ionization of a drug usually affects the lipophilicity and potentially the absorption. Examples from non-critically ill patients include increased gastric pH caused by histamine-2 receptor antagonists or proton pump inhibitors (can be used in the critically ill population for stress ulcer prophylaxis), resulting in decreased absorption of ketoconazole, itraconazole, atazanavir, indinavir, dasatinib, mycophenolate mofetil, cefpodoxime, and dipyridamole. Acid-suppressive drugs increased nifedipine and digoxin absorption, and alendronate had a 2-fold increase in bioavailability in the presence of these agents (Aliment Pharmacol Ther 2009;29:1219-29). Additionally, drug coating or extended release matrices may be altered by pH changes and could potentially impact oral absorption. For example, coadministration of a proton pump inhibitor with enteric coated ketoprofen altered the maximum concentration and time to maximum concentration. Drug absorption depends on the drug's solubility and ability to permeate the intestinal mucosa. The distal end of the feeding tube can be in the stomach, duodenum, or jejunum. Many drugs must be administered into the stomach or duodenum so that they can be properly dissolved by gastric juices, bile, and pancreatic enzymes and can be fully absorbed through the intestines. Thus, drugs like warfarin, which is absorbed high up in the small bowel, and oral iron, which is dissolved in the stomach and absorbed in the duodenum, might not be properly absorbed if they are administered via a jejunostomy tube.

G. Important Considerations for Absorption
1. The overall uncertainty of a patient's ability to absorb drugs from the GI tract often results in the clinician's avoidance of enterally administered drugs because they want to ensure adequate bioavailability. The decision to use the GI route of administration is arbitrary, and in some cases this approach may be more costly. Many clinicians anecdotally use tolerance of enteral feedings as a surrogate marker for normal drug absorption. The definition of tolerance is debatable and assessment of tolerance is highly variable, so it is not an ideal maker for drug absorption. If a drug known to interact with enteral nutrition requires enteral administration, nutrition should be interrupted for the minimum duration possible around drug administration.
2. Subcutaneous and intramuscular routes of administration present similar problems with absorption, but clinical practice has not abandoned these routes of administration. Some clinicians advocate using larger doses of drugs being administered subcutaneously, but no studies have verified the safety or efficacy of this practice. Small studies investigating enoxaparin dosing in medically ill and trauma patients with obesity found improved anti-Xa serum concentrations when using a weight-based dosing method (0.5 mg/kg every 12 hours) compared with standard dosing. This suggests that larger subcutaneous fat distribution can alter the pharmacokinetics and PD of some medications (Thromb Res 2010;125:220-3; Am J Surg 2013;206:847-51).

Patient Case

2. I.L. is a 32-year-old man receiving stress ulcer prophylaxis with esomeprazole 40 mg intravenously every day. Which drug will most likely have an increased absorption secondary to the increased gastric pH?
   - A. Carvedilol.
   - B. Ciprofloxacin.
   - C. Diazepam.
   - D. Digoxin.

IV. DISTRIBUTION

A. The volume of distribution (Vd) of a drug is a PK variable that relates the total amount of drug in the body to the concentration of drug in the serum. A simple mathematical representation of this relationship is the following equation:

$$C = \frac{\text{dose}}{\text{Vd}}$$

where C is the initial serum concentration of an intravenously administered drug and Vd is the volume of distribution. However, the distribution of most drugs is more complex and is affected by several factors such as systemic and tissue perfusion, degree of protein binding, tissue permeability, drug lipid solubility, drug pKa, and pH of the environment. Critically ill patients may be subjected to one or more changes in the previously stated factors that could result in an altered Vd for some drugs.

B. Tissue Perfusion – As noted in the previous section, shock states and vasopressor use can cause a redistribution of blood flow. This results in decreased perfusion of the muscle, skin, and splanchnic organs. Hydrophilic drugs with a smaller Vd (ones that remain in the plasma water volume) may have decreased distribution to physiological compartments with decreased blood flow. This is highlighted by animal studies of septic shock showing lower gentamicin concentrations in the microcirculation than in the central vessels.

C. Fluid Shifts and Tissue Membrane Permeability – Critically ill patients can receive significant volumes of intravenous fluid for resuscitation. This often results in increased total body water and interstitial volume. In addition to fluid administration, diseases such as sepsis, thermal injury, acute respiratory distress syndrome, AKI, heart failure, and cirrhosis can increase interstitial fluid volumes. Moreover, surgery increases extracellular volume postoperatively. In this setting, the Vd for hydrophilic drugs is increased, whereas the Vd for lipophilic drugs is often unchanged. The increased interstitial water provides a larger compartment for hydrophilic drugs to distribute, thus decreasing the serum concentrations. In addition, because distribution is into a larger interstitial space (as the result of increased interstitial water), the drug concentration can be decreased in this space. This has been shown in microdialysis studies evaluating subcutaneous tissue concentrations for intravenously administered piperacillin. Compared with healthy volunteers, patients with septic shock had reduced piperacillin tissue concentrations. However, the increased Vd of drugs is not universally noted with increased interstitial fluid volumes in some critically ill patients. Although one study found increases in aminoglycoside Vd, another study was unable to correlate fluid shifts with changes in the aminoglycoside Vd in critically ill surgical patients (Crit Care Med 1988;16:327-30).

D. Protein Binding – Many drugs are bound to serum protein carriers such as albumin, AAG, lipoproteins, and cortisol-binding protein. Albumin and AAG are particularly important in critically ill patients because albumin usually binds to acidic drugs (e.g., diazepam, phenytoin), whereas AAG binds to basic drugs (e.g., lidocaine, diltiazem). Of importance, albumin concentrations usually decrease (negative acute phase reactant) under stress, while AAG concentrations increase (positive acute phase reactant). The following equation represents the calculation of Vd:

$$\mathrm{Vd} = \left(\frac{f_u}{f_{ut}}\right)\mathrm{Vt} + \mathrm{Vp}$$

where f_u is the fraction unbound in the plasma, f_{ut} is the fraction unbound in the tissues, Vt is the volume of tissue, and Vp is the volume of plasma. When the plasma concentration of albumin decreases, the f_u of a drug increases. This increase results in an increased Vd. Conversely, increases in AAG plasma concentrations decrease the f_u of a drug bound to AAG due to increased protein binding, ultimately decreasing the Vd for that drug.

1. The clinical relevance of this was noted when a decrease in the Vd of lidocaine correlated with an increase in AAG in post-cardiac surgery patients. It was suspected that arrhythmias were caused by these PK changes (Clin Pharmacol Ther 1984;35:617-26). A similar effect has been reported where development of hypoalbuminemia was associated with elevated free valproate concentrations (Crit Care Explor 2022;4:e0746).
2. Table 1 provides examples of drugs used in critically ill patients that bind to albumin and AAG.

Table 1. Extraction Ratio (ER) and Protein Binding of Select Drugs Used in Critically Ill Patients

Protein Binding	High ER Drugs[a]	Intermediate ER Drugs[a]	Low ER Drugs[a]
Albumin	Diltiazem Morphine Propofol Propranolol Verapamil	Aspirin Carvedilol Midazolam Omeprazole	Carbamazepine Ceftriaxone Dexamethasone Diazepam Itraconazole Phenytoin Valproic acid Warfarin
AAG	Diltiazem Fentanyl Lidocaine Propranolol Verapamil	Midazolam	Carbamazepine

[a] ER is addressed in section V. Metabolism.

AAG = α_1-acid glycoprotein.

E. pH – Acid-base disorders are common among the critically ill population. Although these disorders are treatable, they create plasma pH changes that could affect drug distribution. Most drugs are either weak acids or bases and exist in either the ionized or the nonionized state, depending on the surrounding environment. Nonionized drugs penetrate cell membranes more easily than do ionized drugs. Therefore, a drug in the ionized state would be expected to have a smaller Vd than when in the nonionized state. Theoretically, a drug that is a weak acid in a patient experiencing acidemia would be expected to have a larger Vd, whereas a basic drug would have a smaller Vd in the same patient. Although the potential exists to correlate plasma pH changes with changes in drug Vd, evidence in humans is lacking.

F. Extracorporeal Membrane Oxygenation – Use of extracorporeal membrane oxygenation (ECMO) in critically ill patients has increased over the years. Depending on the institution and clinician expertise, ECMO can play a significant role in the care of critically ill patients with respiratory and/or circulatory failure. With implementation of this therapy, changes in the PK of medications have been described. The most common alteration reported is an increase in Vd. Use of ECMO therapy consists of a large volume of blood being extracted from the patient through catheter tubing (generally polyvinyl chloride), circulated through an oxygenator and a heat exchanger before the newly oxygenated blood is returned to the patient. Depending on the type of circuit and/or pump used for ECMO, the volume required to prime the circuit can increase the Vd of some commonly used medications, especially those with a small Vd. Of importance, data on PK changes related to ECMO initiation remain limited. Most of the available data are in neonatal and pediatric patients; however, experience during the COVID-19 pandemic has led to more insight in the adult population. Prospective studies in adults include evaluations of oseltamivir, vancomycin, and meropenem (AACN Adv Crit Care 2018;29:246-58). According to the prospective data, the degree of change in drug distribution created by ECMO may be less than that found in retrospective studies, at least for the studied medications. The generally anticipated pharmacokinetic changes created by ECMO are the result of three factors: (1) the ECMO circuit tubing and membrane oxygenator may bind medications, causing drug sequestration, and the resulting PK change expected is an increased Vd; (2) circuit priming fluid type, fluid pH, and volume potentially increase in medication Vd; and (3) as the ECMO circuit ages, medication binding becomes saturated, creating a scenario in which patient medication requirements may return back to pre-ECMO dosing. Several ex vivo studies have demonstrated loss of drug in the ECMO circuit, including fentanyl and midazolam. This effect should prompt clinicians to monitor patients closely for proper analgesia and sedation during ECMO treatment (Crit Care 2015;19(1):40., Intensive Care Med 2007;33:1018-1024). Other PK changes expected with ECMO relate to the critically ill state of the patient and are discussed throughout this chapter. Of note, these concepts are generalizations, and data for specific drugs may differ. For example, an ex vivo study investigating drug binding to ECMO circuits found that ciprofloxacin recovery rates were 96%, even though the drug was lipophilic and expected to bind to circuit tubing (Crit Care 2015;19:164). A prospective, observational, pilot study evaluated β-lactam and aminoglycoside PK parameters in patients receiving ECMO. Study results showed variable achievement of PK objectives, which led the authors to recommend therapeutic drug monitoring for patients receiving ECMO concurrently with β-lactam or aminoglycoside antibiotics (Anaesth Crit Care Pain Med 2019;38:493-97). Physiochemical properties of the drug molecule also determine the interaction with the circuit. Compound characteristics that should be considered include pKa and degree of ionization, molecular size, plasma protein binding, and lipophilicity. Drug lipophilicity is often reported through the n-octanol/water partition coefficient, or logP, whereas a high logP indicates a more lipophilic compound at higher risk of ECMO circuit sequestration. Protein binding and the extent thereof may also influence the extent of drug sequestration in the ECMO circuit (Crit Care 2015;19:164). The COVID-19 pandemic often necessitated the use of ECMO and revealed pharmacokinetic changes in several antiviral agents. Changes in Vd were found for favipiravir and ribavirin. Suspected alterations in cytochrome P450 metabolism were noted for chloroquine, lopinavir, ritonavir, and favipiravir. The reader is referred to a comprehensive review by the European Society of Clinical Microbiology, Infectious Diseases (Clin Pharmacokinet 2020;59:1195-16) for more information about the impact of COVID-19 and ECMO on the pharmacokinetics of antivirals.

Patient Cases

3. R.H. is 20-year-old man who presents to the emergency department with nausea and vomiting. His vital signs are significant for heart rate 130 beats/minute, blood pressure 98/62 mm Hg, and respiratory rate 28 breaths/minute. Laboratory tests reveal an arterial blood gas significant for a pH of 7.11, Pco_2 of 18 mm Hg, and bicarbonate of 5.2 mEq/L. His basic metabolic panel is significant for potassium concentration 5 mEq/L, BUN 22 mg/dL, SCr 1.4 mg/dL, and blood glucose 400 mg/dL. Which changes would be most likely to occur in the Vd of a weak acid like ciprofloxacin in this patient?
   A. Increased because of decreased ionization.
   B. Decreased because of increased ionization.
   C. No change because of no change in ionization.
   D. Decreased because of decreased ionization.

4. B.B. is a 62-year-old woman admitted to the ICU for septic shock. She has received 6 L of crystalloids in the past 24 hours, including her initial resuscitation and maintenance fluids. The Vd for which one of the following antibiotics would most likely be unaffected by the amount of intravenous fluids administered?
   A. Tobramycin.
   B. Daptomycin.
   C. Levofloxacin.
   D. Cefepime.

V. METABOLISM

A. Introduction – The predominant location for drug metabolism is the liver, but it can include tissues such as the GI tract, kidneys, lung, and brain. The greatest extent of knowledge regarding drug metabolism and, more importantly, changes in critically ill patients relates to hepatic metabolism. Therefore, this section will focus largely on changes in the hepatic metabolism of drugs, specifically high and low extraction ratio drugs. However, the next section briefly discusses renal metabolism because the clinical ramifications of drug metabolism in the kidney are a potential area for future research.

B. Renal Metabolism – There is evidence that the kidneys express the CYP isoenzymes 2B6 and 3A5. Data suggest that CYP 2C8, 2C9, and 3A4 are also expressed in the kidneys. In addition, UGT (UDP-glucuronosyltransferase) enzymes 1A9 and 2B7 are abundantly expressed in the kidneys and play a role in the glucuronidation of drugs. However, no data describe how changes in critically ill patients affect drug metabolism in the kidneys by these enzymes. As evidenced by increased hypoglycemic events and lower insulin requirements in critically ill patients with AKI, clinically relevant changes in renal insulin metabolism occur, but the exact mechanisms for these are not well characterized (Nutrition 2011;27:766-72).

C. Hepatic Metabolism – Hepatic clearance refers to the volume of blood that is completely cleared of drug by the liver per unit of time. The ability of the liver to metabolize drugs depends on three physiologic variables: hepatic blood flow, drug protein binding, and the intrinsic activity of hepatic enzymes. When evaluating an intravenously administered drug (bioavailability of 1), clearance by the liver can be simply represented by the following equation:

$$CL_H = Q \times E$$

where CL_H is the hepatic clearance, Q is the hepatic blood flow, and E is the hepatic extraction ratio. The hepatic extraction ratio can further be described by the following equation:

$$E = \frac{f_u \times CL_{int}}{Q + f_u \times CL_{int}}$$

where f_u is the fraction unbound in the plasma, CL_{int} is the intrinsic hepatic clearance, and Q is hepatic blood flow. The hepatic extraction ratio is classified by the fraction of drug removed during one pass through the liver and can range from 0 to 1. It can be separated into high (greater than 0.7), intermediate (0.3–0.7), and low (less than 0.3) categories. The extraction ratio would be zero when the liver does not metabolize a drug and 1 when CL_H depends entirely on hepatic blood flow. The effect of changes in critical illness depends on the extraction ratio of the drug. Table 1 lists select high extraction ratio and low extraction ratio drugs.

D. High Extraction Ratio Drugs

1. Drugs with a high hepatic extraction ratio are metabolized by hepatic enzymes and are thus cleared by the liver. In drugs with high extraction ratios, clearance does not vary with changes in hepatic enzymatic activity and is primarily limited by hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} >>> Q$$

Given the previously stated relationship, CL_H can be simplified to:

$$CL_H = Q$$

As previously noted, clearance of a drug pertains to removal of the drug from the blood. Therefore, the effect on plasma drug concentration will affect the efficacy of the drug. Because an unbound or "free drug" elicits the pharmacological response, the unbound steady-state concentration (C_{ssu}) is important to assess. The total concentration, otherwise called the steady-state concentration (C_{ss}) of hepatically metabolized drugs, can be represented by the following equation:

$$C_{ss} = \frac{dose}{CL_H}$$

where C_{ss} is the steady-state concentration (for both protein bound and unbound drugs) and dose is the rate of drug input. Because $CL_H = Q$ for high extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{dose}{Q}$$

The unbound steady-state concentration for a high extraction ratio is represented by the following equation:

$$C_{ssu} = \frac{f_u \times dose}{Q}$$

Figure 1 shows how a change in each variable of CL_H affects the C_{ss} and C_{ssu}. For high extraction ratio drugs, altered hepatic blood flow affects both the C_{ss} and the C_{ssu}, whereas changes in f_u affect only the C_{ssu}.

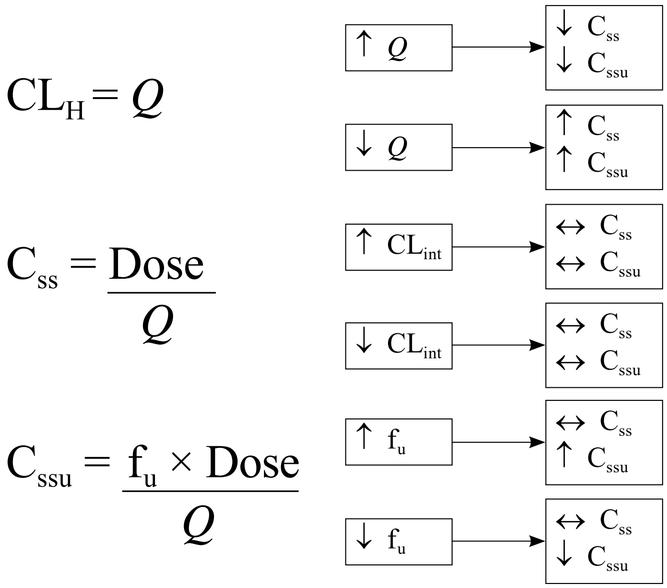
$CL_H = Q$
$C_{ss} = \frac{Dose}{Q}$
$C_{ssu} = \frac{f_u \times Dose}{Q}$
↑ Q → ↓ C_{ss} ↓ C_{ssu}
↓ Q → ↑ C_{ss} ↑ C_{ssu}
↑ CL_{int} → ↔ C_{ss} ↔ C_{ssu}
↓ CL_{int} → ↔ C_{ss} ↔ C_{ssu}
↑ f_u → ↔ C_{ss} ↑ C_{ssu}
↓ f_u → ↔ C_{ss} ↓ C_{ssu}

Figure 1. Effect of variable changes on steady-state and unbound steady-state concentrations of a high extraction ratio drug.

2. Effect of increased hepatic blood flow: Animal models have shown a clear increase in splanchnic perfusion during the hyperdynamic phase of sepsis. Critically ill patients in the hyperdynamic phase of sepsis or septic shock have an increased cardiac output and increased hepatosplanchnic blood flow. However, no correlation directly relating cardiac output (or an increase in cardiac output) with an increase in splanchnic blood flow could be established in some studies. Therefore, quantification of the increase in blood flow and the resultant increase in hepatic metabolism cannot be established. The clinician is left to assume the potential for increased metabolism of high extraction ratio drugs and the expected decrease in unbound steady-state concentration and possibly a reduced clinical efficacy.
   a. Any condition or therapy that increases cardiac output could theoretically improve hepatic blood flow. Although data in humans are lacking, an animal model of endotoxemia showed improved hepatic blood flow after dobutamine.
3. Effect of decreased hepatic blood flow
   a. Conditions with a low cardiac output such as hypovolemic or hemorrhagic shock, decompensated sepsis, myocardial infarction with or without cardiogenic shock, and acute heart failure exacerbation would be expected to cause a decrease in hepatic blood flow. Human studies to verify this assertion are lacking. Animal models of decompensated sepsis and cardiogenic shock show reduced hepatic blood flow, which would be expected to increase the C_{ssu} and potentially increase the effect of, or produce toxicity for, drugs with high extraction ratios.
   b. Mechanical ventilation has been noted to increase or decrease cardiac output and subsequently hepatic blood flow, depending on the patient's condition. Mechanical ventilation may also decrease cardiac output and subsequently hepatic blood flow because of increased intrathoracic pressure. This pressure causes a decrease in venous return to the heart, compresses the ventricles, and reduces ventricular filling. The result is a decrease in cardiac output (N Engl J Med 1981;304:387-92) and hepatic blood flow (Crit Care Med 1982;10:703-5). Mechanical ventilation may increase cardiac output in patients with hypervolemic heart failure by reducing afterload (Ann Transl Med. 2018;6(18):349).

E. Low Extraction Ratio Drugs – Drugs with a low hepatic extraction ratio undergo a lower degree of hepatic enzyme metabolism; therefore, clearance is limited by hepatic enzymatic activity, and clearance is independent of hepatic blood flow. Mathematically, this can be represented by:

$$f_u \times CL_{int} <<< Q$$

According to this relationship, CL_H can be simplified to:

$$CL_H = f_u \times CL_{int}$$

Again, the C_{ss} for hepatically metabolized drugs can be represented by the following equation:

$$C_{ss} = \frac{dose}{CL_H}$$

where C_{ss} is the steady-state concentration and dose is the rate of drug input. Because $CL_H = f_u \times CL_{int}$ for low extraction ratio drugs, the equation can be modified to:

$$C_{ss} = \frac{dose}{f_u \times CL_{int}}$$

The unbound steady-state concentration for a low extraction ratio drug is represented by the following equation:

$$C_{ssu} = \frac{dose}{CL_{int}}$$

Figure 2 shows how a change in each variable of CL_H affects the C_{ss} and the C_{ssu}. For low extraction ratio drugs, altered CL_{int} affects both the C_{ss} and the C_{ssu}, whereas changes in the f_u affect only the C_{ss}.

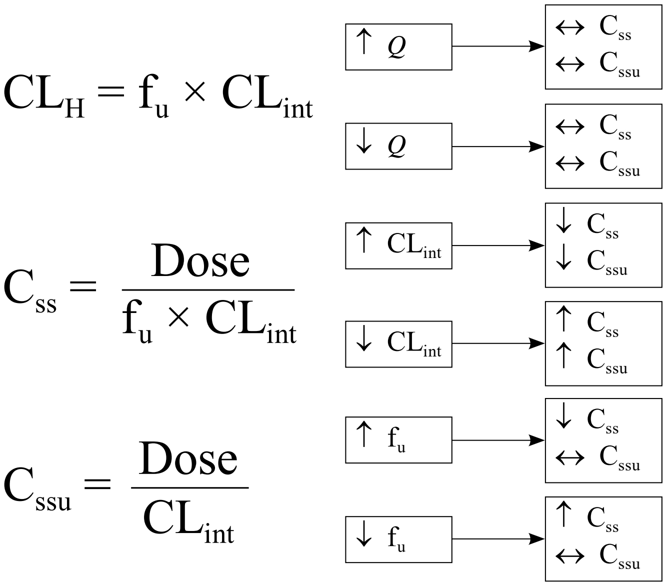

Figure 2. Effect of variable changes on steady-state and unbound steady-state concentrations of a low extraction ratio drug.

F. Effect of Changes in Intrinsic Clearance
   1. Drug interactions – A major mechanism for altered intrinsic clearance is not caused by changes in critical illness, but still poses a significant threat to altered metabolism of drugs. The CYP enzymes play an important role in phase I metabolism. Many drugs used in critically ill patients are substrates, inducers, inhibitors, or combinations of these. Critically ill patients often have complex pharmacotherapeutic regimens that create the potential for drug interactions through the CYP system. As in other patient populations, drug concentrations are increased when substrates are coadministered with inhibitors of the same CYP and decreased when substrates are coadministered with inducers.
   2. Inflammation – Inflammatory states play an important role in altering CYP activity. The inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor alpha decrease the expression and activity of CYP enzymes. Similarly, patients in early sepsis would have increased inflammatory cytokines with the resultant depressed CYP activity. This is supported by studies showing that endotoxin administration results in decreased CYP-mediated drug metabolism in healthy volunteers. However, studies have not characterized a time course for the cytokine-mediated changes. Clinicians are left to use patient response and monitoring for toxicity to determine whether drug metabolism is altered or has returned to normal.
   3. Hypothermia – Animal models have shown that hypothermia affects drugs metabolized through the CYP system. Drugs studied in animal models include fentanyl, pentobarbital, propranolol, and morphine. Human studies have investigated the effect of hypothermia on low extraction ratio drug kinetics. One example showed changes in phenytoin PK during mild hypothermia. Specifically, increased concentrations and reduced metabolism, but no changes in protein binding, were noted during hypothermia (Ther Drug Monit 2001;23:192-7). Other drugs noted to have decreased hepatic clearance during hypothermia are midazolam, fentanyl, remifentanil, phenobarbital, and vecuronium.
   4. AKI – One study investigated the effects of AKI on the hepatic metabolism of midazolam. Patients with worsening AKI, as determined using the RIFLE (risk, injury, failure, loss, end-stage kidney disease) criteria, had increasing midazolam concentrations. The authors hypothesized that the increased concentrations were caused by impaired CYP3A activity (Intensive Care Med 2012;38:76-84).

G. Intermediate Extraction Ratio Drugs – Metabolism of an intermediate extraction ratio drug depends on hepatic blood flow, intrinsic clearance, and fraction of unbound drug. Essentially, intermediate extraction ratio drugs depend on the same variables as both the low extraction ratio and high extraction ratio drugs. As such, they are the most complex drugs for determining how hepatic clearance will be affected in critically ill patients. This is important because critically ill patients usually have more than one change occurring at the same time. For example, patients with septic shock may have increased hepatic blood flow secondary to increased cardiac output while having a decreased intrinsic clearance secondary to increased circulating inflammatory cytokines. Quantifying the overall effect is difficult in the ever-changing critically ill patient. The clinician is often left to monitor for the expected therapeutic outcome while being aware of the potential toxicities. Table 1 lists select intermediate extraction ratio drugs.

H. Other Factors
   1. TBI increases the hepatic clearance of some drugs.
      a. One study found that patients with TBI had increased hepatic clearance of phenytoin during the first 7–14 days. The authors alluded to the possibility that the increased clearance was associated with changes in protein binding, induction of metabolism, or stress on hepatic metabolic capacity (Clin Pharmacol Ther 1988;44:675-83).
      b. Another study noted a correlation between nutritional protein intake and increased phenytoin metabolism in patients with TBI.

   c. Phase II enzymatic activity may also be enhanced in patients with TBI, as evidenced by increased lorazepam clearance. Similar data for lorazepam were noted in thermally injured patients. These data suggest that phase II metabolism can be affected by critical illness.

2. Hepatic failure – Hepatic failure will significantly affect drug dosing in the critically ill patient. See the Hepatic Failure/GI/Endocrine Emergencies chapter for more information regarding drug dosing in hepatic failure.

Patient Cases

5. A.P. is a 35-year-old woman admitted to the ICU for an acute asthma exacerbation. She was intubated and required mechanical ventilation. She is prescribed morphine for pain control. Which best describes the effect of mechanical ventilation on morphine unbound concentrations?

   A. Increases oxygenation delivery to the liver and increases the unbound concentration.
   B. Decreases hepatic blood flow and increases the unbound concentration.
   C. Increases cytokine production and decreases the unbound concentration.
   D. Cannot affect the unbound concentration.

6. J.M. is a 34-year-old woman admitted to the ICU with new-onset sepsis. She was continued on her home medication, diazepam, for anxiety. She is empirically initiated on vancomycin 1 g intravenously every 12 hours, piperacillin/tazobactam 3.375 g intravenously every 6 hours, and fluconazole 400 mg intravenously every 24 hours. Which PD response would you most expect in J.M.?

   A. Increased risk of anxiety caused by an increased intrinsic clearance of diazepam.
   B. Increased risk of sedation caused by a decreased intrinsic clearance of diazepam.
   C. Increased risk of anxiety caused by a decreased unbound fraction of diazepam.
   D. Increased risk of sedation caused by an increased unbound fraction of diazepam.

7. P.M. is receiving phenytoin for the treatment of posttraumatic seizures. The measured total phenytoin concentration is 8 mcg/mL. You calculate the adjusted concentration according to P.M.'s hypoalbuminemia (albumin of 2.5 g/dL) and determine the concentration to be approximately 13 mcg/mL. Which of the following relationships best describes why an adjusted total phenytoin concentration must be calculated?

   A. The phenytoin C_{ssu} is increased because of an increase in the f_u.
   B. The phenytoin C_{ss} is increased because of an increase in f_u.
   C. The phenytoin C_{ssu} is decreased because of an increase in f_u.
   D. The phenytoin C_{ss} is decreased because of an increase in f_u.

8. C.P. is a 50-year-old man admitted to the medical ICU for management of diabetic ketoacidosis. His medical history is significant for hypertension, type 1 diabetes, and a myocardial infarction 2 years ago. He quit smoking last year and drinks alcohol occasionally. His vital signs are significant for heart rate 125 beats/minute, blood pressure 95/65 mm Hg, and respiratory rate 22 breaths/minute. His significant hypovolemia contributed to the development of AKI. His current SCr is 2.8 mg/dL. His blood glucose is significantly elevated at 350 mg/dL. He will be initiated on a continuous intravenous infusion of insulin to correct his blood glucose. Which factor is most important to consider when dosing insulin in C.P.?

   A. Decreased renal metabolism of insulin.
   B. Increased Vd of insulin.
   C. Increased hepatic metabolism of insulin.
   D. Decreased receptor binding of insulin.

VI. EXCRETION

A. Renal Excretion

1. For most drugs, the kidneys are the primary site for excretion of the parent drug, metabolites, or both. Urinary excretion of a drug depends on filtration, secretion, and reabsorption. Patients in the ICU may have increased, decreased, or normal renal excretion of drugs. The state of renal excretion depends on many variables and can change rapidly. This is especially true in ICU patients, for whom a clinical condition can contribute to both increased and decreased excretion, depending on how that condition progresses.
2. Filtration
    a. Glomerular filtration rate (GFR) is the variable most widely used to describe kidney function. The National Kidney Foundation defines normal kidney function as 140 ± 30 mL/minute/1.73 m^2 for healthy young men and 126 ± 22 mL/minute/1.73 m^2 for healthy young women. Although there is no standard definition for increased GFR, an increase of 10% above the upper end of normal (greater than 160 mL/minute/1.73 m^2 in men and greater than 150 mL/minute/1.73 m^2 in women) has been proposed (Crit Care 2013;17:R35).

    b. ARC – Conditions such as surgery, trauma, burns, and early sepsis have been associated with increased renal blood flow. This is usually believed to be caused by an increased cardiac output coupled with vasodilation. The resulting ARC is believed to be a response to an inflammatory insult (e.g., systemic inflammatory response syndrome).
        i. One study found glomerular hyperfiltration in 17.9% of patients admitted to the ICU. Most of these patients were younger and admitted for multi-trauma or surgery (Anaesth Intensive Care 2008;36:674-80). These data are supported by a study showing young, postoperative trauma patients with peak creatinine clearance (CrCl) values as high as 190 mL/minute/1.73 m^2. A more recent study found significant risk factors for the ARC to be age 50 or younger, trauma, and a modified sequential organ failure score of 4 or less. Finally, a study of 133 trauma patients found age 56 or younger, SCr less than 0.7 mg/dL, and male sex to be independent risk factors for ARC. From this, study investigators developed a model to predict ARC in patients, the ARC in trauma intensive care (ARCTIC) score. A score of 6 or higher had a sensitivity of 0.843, a specificity of 0.682, a positive predictive value of 0.843, and a negative predictive value of 0.682.

        ii. A study of burn patients found an increase in iohexol clearance with a median value of 155 mL/minute/1.73 m^2 on day 1 of admission. In this small study, clearance had returned to the expected baseline of 122 mL/minute/1.73 m^2 by day 7 (Burns 2010;36:1271-6). In addition, several studies have shown increased excretion of renally eliminated drugs in burn patients, likely related to the second phase (hyperdynamic) of burn injury, which generally begins 48 hours after the burn injury. Examples include vancomycin, ciprofloxacin, imipenem, fluconazole, and aminoglycosides.

        iii. Fluid administration would be expected to improve cardiac output and thus renal blood flow. Animal studies have confirmed that the administration of crystalloids can transiently increase CrCl. Sheep administered normal saline and 3% hypertonic saline have a significantly higher calculated CrCl than controls. However, no human studies have verified ARC in critically ill patients after fluid administration.

        iv. Vasoactive drugs would be expected to improve cardiac output and thus renal blood flow. However, studies of humans did not corroborate this expectation and, instead, were only able to establish an improvement in CrCl in a subset of patients with impaired CrCl before norepinephrine administration. Although studies were unable to show development of ARC, patients receiving vasopressors for shock states might be expected to have normal renal blood flow and CrCl, assuming they are not experiencing AKI. The duration of ARC is not well established, but the peak CrCl appears to occur at about days 4–5 in most studies, with CrCl returning to normal by day 7 in one study.

c. Impaired renal clearance
   i. Decreased renal excretion of drugs during AKI is the most widely applicable change occurring in critically ill patients. Depending on the patient population and definition used, the incidence of AKI in ICU patients can be as high as 78%. AKI significantly affects the excretion of renally eliminated drugs, and dosing modifications must be made in these situations to avoid potential toxicity.
   ii. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI recommend that staging of AKI be done using the KDIGO AKI criteria. However, these guidelines have no specific recommendations regarding drug dosing.
   iii. A clinical update to the 2010 KDIGO guidelines does recommend how to approach drug dosing in critically ill patients with AKI. Because of the complicated picture of AKI in critically ill patients, however, these recommendations are not as precise as the recommendations for drug dosing in CKD. In fact, the authors note that most renal dose adjustment recommendations in the literature and from the FDA (U.S. Food and Drug Administration) are based on data from patients with CKD (Kidney Int 2011;80:1122-37).
   iv. The update recommends a stepwise approach to adjusting drug-dosing regimens in patients with AKI (Box 2).

Box 2. Recommended Steps for Assessing and Adjusting Drug Regimens in Patients with AKI

Step 1 – Assess the following
- Demographic information
- Medical history (including history of renal disease)
- Current clinical information
- Current laboratory information
- DNA polymorphisms

Step 2 – Estimate GFR (use the best equation according to patient factors)
- Age
- Body size
- Ethnicity
- Concomitant diseases

Step 3 – Review current medications
- Identify drugs needing individualized dosing

Step 4 – Calculate individualized treatment regimen
- Determine treatment goals (PK or PD values)
- Calculate dosage regimen (according to drug PK and changes noted in the patient)

Step 5 – Monitor regimen
- Drug response
- Signs or symptoms of toxicity
- Drug concentrations (if available)

Step 6 – Revise regimen
- Adjust regimen according to patient response
- Adjust regimen according to changes in patient status

AKI = acute kidney injury; GFR = glomerular filtration rate; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

v. The recommendations include using the estimated GFR (eGFR) or CrCl to assess renal function for drug dosing. The update provides several equations that can be used to estimate kidney function, including the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations with a stronger emphasis on CKD-EPI over MDRD by the National Kidney Foundation. Recent evidence has suggested the removal of race adjustment in CKD-EPI, and MDRD has improved bias, accuracy, and precision of eGFR equations in Black adults (*Am J Health Syst Pharm*. 2024; Nov 18:zxae317.). The CKD-EPI equation can be calculated as follows:

$$\text{GFR}_{\infty} = 142 \times \min(\text{SCr} / \kappa, 1)^{\alpha} \times \max(\text{SCr}/ \kappa \;\; 1)^{-1.2} \times 0.9938^{\text{Age}} \times 1.012 \text{ (if female)}$$

where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.241 for females and −0.302 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1 (Am J Kidney Dis 2022;80:691-6).

vi. The Cockcroft-Gault equation is used to estimate the CrCl as follows:

$$\text{CrCl} = \frac{(140 - \text{age})\,\text{weight}}{\text{SCr} \times 72} \times 0.85 \text{ (if female)}$$

where CrCl is in milliliters per minute, weight is in kilograms, and SCr is in milligrams per deciliter.

vii. The MDRD equation is described as follows:

$$\text{GFR} = 175.6 \times \text{SCr}/88.4^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)}$$

where GFR is in milliliters per minute/1.73 m^2, SCr is measured in the laboratory using isotope dilution mass spectroscopy (IDMS), and age is in years.

viii. The update also notes that the most important factor when determining kidney function is having at least one GFR estimate for all patients.

3. Secretion and reabsorption can play important roles in drug concentration and clearance. However, it is difficult to study changes in drug secretion and reabsorption in patients. Therefore, data are not available to describe the clinically important changes in these two variables in critically ill patients.
4. Kidney replacement therapies (KRTs): See the Acute Kidney Injury chapter for more information regarding KRT and drug dosing.
    a. Patients receiving KRT with a diagnosis of AKI may require hemodialysis and/or hemofiltration. The choice of dialytic technique depends on the institution, clinician expertise, patient hemodynamic stability, profile, and access to various types of renal replacement machines. Drug removal by dialysis depends on dialytic method.
    b. Acute intermittent hemodialysis: Intermittent hemodialysis can significantly contribute to the elimination of drugs, whereas other drugs are not appreciably removed by hemodialysis. Removal of drugs during hemodialysis depends on the size of the molecule, Vd, protein binding, and type of dialysis filter (specifically the membrane size).
    c. Continuous KRTs (CKRTs): CKRT refers to several different methods of renal replacement therapy. Many studies have investigated the effect of CKRT on drug removal. Considerable variability exists in the type of CKRT used. The 2010 clinical update to the KDIGO guidelines suggests the following equation as one option to determine the appropriate drug dose in CKRT:

$$\text{dose} = \text{dose}_n \left(\frac{CL_{nonrenal} + (Q_{eff} \times SC)}{CL_{norm}} \right)$$

where dose is the desired dose for CKRT, dose n is the normal dose of a drug, $CL_{nonrenal}$ is the nonrenal clearance of a drug, Q_{eff} is the effluent rate, SC is the sieving coefficient, and CL_{norm} is the normal clearance of the drug. As the effluent rate (in milliliters per minute) increases, so does solute clearance. Therefore, it is the most important CKRT parameter pertaining to drug removal.

B. Hepatic Excretion – Hepatic excretion of drugs is less important for most drugs than renal excretion. However, excretion of drug in the bile can potentially be affected by critical illness. This is evidenced by changes in the clearance of some neuromuscular blocking agents.

1. A study of nine patients undergoing surgery for total biliary obstruction showed a significant increase in pancuronium half-life compared with normal patients (270 minutes vs. 132 minutes, $p<0.001$). The urinary excretion of pancuronium and its metabolites did not change. This suggests that the increased half-life was caused by the decreased hepatic excretion of pancuronium (Br J Anaesth 1977;49:1103-8).
2. Results were similar for vecuronium in patients with cholestasis, in which the mean half-life was 98 minutes in patients with cholestasis and 58 minutes in normal patients (Br J Anaesth 1986;58:983-7).

C. Pulmonary Excretion – Pulmonary excretion is important for volatile gases such as anesthetics. It can be hypothesized that impaired gas exchange (e.g., acute respiratory distress syndrome) affects the body's ability to remove volatile gases. However, data are lacking regarding changes in critically ill patients that affect their ability to excrete anesthetics.

VII. PHARMACODYNAMICS

A. *Pharmacodynamics* refers to the biochemical and physiologic effects of a drug, specifically those related to the mechanism of action.

B. This term also pertains to drug/receptor binding and clinical effect. Most clinicians use the term to refer to the physically identifiable effect of a drug in a patient. For example, the PD effect of an opioid is the relief of pain reported by the patient. However, the PD effect of some drugs is not readily observable. For example, the PD effect of proton pump inhibitors is an increase in gastric pH. Few PD studies of critically ill patients are reported in the medical literature, and most pertain to antibiotic therapy.

1. Antibiotic overview: PD studies of antibiotics use models to estimate the combined effects of the patient population PK of specific antibiotics and the MIC for select bacteria. These techniques usually allow a calculation of the desired PD outcome. Antibiotics generally fall into three PD categories, which correlate with efficacy: (1) time-dependent killing (T>MIC), (2) concentration-dependent killing (C_{max}/MIC), and (3) a combination of time- and concentration-dependent killing (ratio of area under the curve to the minimum inhibitory concentration for the bacterial pathogen [AUC/MIC]).
2. β-Lactam antibiotics: For β-lactam antibiotics, the PD parameter of the free drug concentration time above the MIC (*f*T>MIC) is used to predict treatment success. This is reported as a percentage of time the free drug concentration remains above the MIC. The ideal *f*T>MIC is 100%. However, PD studies of β-lactam antibiotic use in critically ill patients have found that a low percentage of patients will achieve the desired PD targets (Crit Care 2011;15:R206). These failures are often attributed to clinically important changes that can occur rapidly in critically ill patients (e.g., ARC). As such, epidemiologic studies have tried to determine a breakpoint at which clinical success is achieved. Studies vary, and the suggested breakpoint is 50%–100% (*f*T>MIC) (Br J Clin Pharmacol 2012;73:27-36), with others

suggesting cutoffs of about 40% for carbapenems, 50% for penicillins, and 50%–75% for cephalosporins (Clin Infect Dis 2008;26:1-10). Modeling usually suggests improved PD of β-lactams when using prolonged or continuous infusions. Many institutions have adopted the practice of prolonged infusions. This is supported by quasi-experimental and retrospective studies showing improved outcomes such as improved clinical cure, improved microbiological cure, and reduced morbidity and mortality. However, prospective controlled clinical trials have had mixed results (J Crit Care 2014;29:1089-95; Am J Respir Crit Care Med 2015;192:1298-305). There are many reasons why there appears to be a discrepancy between PD modeling studies and controlled clinical trials; patient variability, dosing variability, and disease severity seem to be important factors (Ann Intensive Care 2012;2:37). Another variable to consider is resolving AKI and timely dose adjustment of β-lactam antibiotics because delayed dose adjustments have been associated with in-hospital mortality (Open Forum Infect Dis 2024;11:ofae059).

3. Aminoglycosides: Aminoglycoside bacterial killing is based on the ratio between the maximum drug concentration and the MIC for the bacterial pathogen (C_{max}/MIC), or concentration-dependent killing. Efficacy was noted when patients were pooled from four controlled clinical trials and peak concentrations, MIC values, and clinical response were evaluated. Peak-to-MIC ratios of 8–10 resulted in around a 90% clinical response (J Infect Dis 1987;155:93-9). In patients with gram-negative bacteremia, early therapeutic peak concentrations were a significant discriminating factor for mortality. According to these and other data, once-daily aminoglycoside dosing has been used. Taking advantage of high peak concentrations maximizes the PD of aminoglycosides. Variability in the Vd of aminoglycosides in critically ill patients, together with concern for ARC in this population, raises issues about appropriately dosing these agents, especially in critically injured trauma patients, whose drug concentrations can be undetectable for more than 12 hours (J Trauma 2000;49:869-87) and larger loading doses and more frequent monitoring may be warranted.
4. Vancomycin: The PD parameter that best describes vancomycin efficacy is the AUC/MIC. Several studies have evaluated the free 24-hour AUC/MIC ($f\text{AUC}_{0\text{-}24}$/MIC), or the AUC × 50% protein binding/MIC. Current guidelines use the available literature to recommend an AUC/MIC of 400 or greater for effectiveness and less than 600 for safety. (Am J Health-Syst Pharm 2020;77:835-864). Loading doses of vancomycin of 20–35 mg/kg based on actual body weight are recommended to expedite achieving these target serum concentrations and PD goals while decreasing the chance of subtherapeutic serum concentrations during the initial days of therapy. The guidelines recommending continuous infusion regimens are an acceptable alternative when conventional dosing is unable to achieve the target AUC. They also note the intravenous access issues presented for critically ill patients when continuous infusion regimens are employed (Clin Infect Dis 2020:71;1361-4). Specifically, vancomycin has been demonstrated to be Y-site incompatible with multiple β-lactams, moxifloxacin, propofol, phenytoin, methylprednisolone, and furosemide—all medications that are commonly used in the ICU setting. As such, clinicians should closely monitor vancomycin coadministration with other medications. Of interest is a retrospective study of vancomycin-associated nephrotoxicity in critically ill patients. In this study, intermittent dosing was associated with a significantly higher risk of nephrotoxicity than continuous infusion (odds ratio 8.2; $p<0.001$) (Crit Care Med 2014;42:2527-36). Of note, more aggressive dosing may be required in critically ill patients. Doses as high as 20 mg/kg administered as often as every 6 hours were needed to optimize PK variables in critically injured trauma patients being treated for ventilator-associated pneumonia (J Trauma Acute Care Surg 2012;72:1478-83).
5. Fluoroquinolones: Similar to the efficacy of aminoglycosides, the efficacy of the fluoroquinolones is based on a C_{max}/MIC (10 or greater), and they exhibit a post-antibiotic effect against gram-negative and gram-positive bacteria. PD studies have shown that the $f\text{AUC}_{0\text{-}24}$/MIC is associated with bacterial eradication. In one study of lower respiratory tract infections treated with ciprofloxacin, an $\text{AUC}_{0\text{-}24}$/MIC of 125 was associated with the percent probability for clinical cure of 80% (Antimicrob Agents Chemother 1993;37:1073-81). However, it is difficult to incorporate these PD variables into fluoroquinolone dosing in individual critically ill patients. Measuring fluoroquinolone serum concentrations is not routine; therefore, it is difficult to determine whether the PD targets have been met in an individual patient.

6. Nonantibiotic drugs: PD studies of other drugs in critically ill patients are sparse.
   a. The PD parameter for continuous infusions of many anticoagulants is the change in activated partial thromboplastin time. Unfractionated heparin infusions are predictable in most patient populations. However, in critically ill patients, less than one-half of patients (44%) reached therapeutic activated partial thromboplastin times within 24 hours of heparin infusion initiation (Neth J Med 2013;71: 466-71). Concern for a variable response in critically ill patients has led to the development of modified dosing nomograms/protocols. Researchers have found a shortened time to therapeutic activated partial thromboplastin times in critically ill patients receiving unfractionated heparin and direct thrombin inhibitors (argatroban and bivalirudin) with nomograms.
   b. As with antibiotic PD studies, most PD studies of other drugs have shown a decreased response in critically ill patients. For example, critically ill patients in septic shock had a reduced response to dobutamine compared with those without septic shock and with normal volunteers (Crit Care Med 1993;21:31-9). Trauma patients with edema have lower AUCs for anti-Xa activity than do non-edematous patients (J Trauma 2005;59:1336-43). Mechanically ventilated patients with chronic obstructive pulmonary disease were studied for covariates affecting acetazolamide therapy. Mixed-effects modeling found the Simplified Acute Physiology Score II, serum chloride concentrations, and concomitant corticosteroids to be the main covariates interacting with acetazolamide PD.

VIII. THERAPEUTIC DRUG MONITORING

A. Therapeutic drug monitoring (TDM) refers to the measurement of drug concentrations in the blood. The focus of TDM is on drugs with a narrow therapeutic index and aims to achieve two goals: (1) maximize efficacy and (2) reduce toxicity. Use of TDM in critically ill patients is extremely important because changes in the PK variables previously described can result in less-than-desirable drug concentrations. Table 2 highlights commonly used medications in the ICU and their corresponding therapeutic ranges. One of the main limitations of TDM is the lack of clinically available assays. In addition, assays for some drugs may not be sufficiently cost-effective or timely, thus limiting their routine use in some institutions. These issues usually result in TDM being available for a very limited spectrum of drugs. Although not ubiquitous, TDM is being incorporated more often to assist with PD target attainment. Examples include β-lactam antibiotics and azole antifungals.
   1. Monitoring of blood concentrations depends on the intended use and interpretation of those concentrations. Most TDM occurs as a method to confirm a therapeutic concentration in a patient with signs and/or symptoms of toxicity or decreased efficacy. In this case, a concentration is measured during the appropriate time interval (Table 2), and a clinician interprets the concentration. If needed, the clinician modifies the drug dosing according to clinical experience. This method may produce variable results. Critically ill patients require important considerations. For example, if extended-interval dosing is being used, the likelihood of an increased Vd must be considered. Patients with ARC have the potential to have a prolonged drug-free period. Finally, the status of a critically ill patient can change rapidly. Monitoring for decreased kidney function is essential to avoid accumulation.

Table 2. TDM Ranges for Select Drugs Used in Critically Ill Patients

Drug	Timing of Blood Sample	Therapeutic Range[a]	Unbound Therapeutic Range
Amikacin	Peak (extended interval) Trough (extended interval) Peak (traditional) Trough (traditional)	30–40 mg/L undetectable 20–30 mg/L < 8 mg/L	—
Carbamazepine	Trough	4–12 mg/L	0.5–4 mcg/mL
Cyclosporine	Trough	50–500 mcg/L	—
Digoxin	Trough (8–24 hr postdose)	0.6–2 mcg/L	0.4–0.9 ng/mL
Gentamicin	Peak (extended interval) Trough (extended interval) Peak (traditional) Trough (traditional)	5–20 mg/L undetectable 8–10 mg/L < 2 mg/L	—
Lidocaine	Peak	1.5–5 mg/L	—
Phenobarbital	Trough	10–40 mg/L	—
Phenytoin	Trough	10–20 mg/L	1–2.5 mcg/mL
Tobramycin	Peak (extended interval) Trough (extended interval) Peak (traditional) Trough (traditional)	5–20 mg/L undetectable 8–10 mg/L < 2 mg/L	—
Valproate	Trough	50–100 mcg/mL	5v15 mcg/mL[b]
Vancomycin	Peak and Trough to calculate AUC	AUC 400–600 mg × hour/L	—

[a] Therapeutic ranges for antibiotics may be modified on the basis of pharmacodynamic target attainments (e.g., peak to MIC ratio).

[b] Optimal range for unbound valproate remains undetermined.

TDM = therapeutic drug monitoring.

Data adapted from: J Antimicrob Chemother 2016;71:2754-9; Clin Infect Dis 2020:71;1361-4; Ther Drug Monit 2017;39:522-30; Infect Dis 2023;10:ofad058; Pharmacotherapy 2008;28:1391-400; Am J Cardiol 2012;109:1818-21.

2. For certain intravenously administered drugs (e.g., aminoglycosides, vancomycin), several concentrations can be measured when the drug is at steady state. The patient’s specific PK can be determined and used to tailor the drug-dosing regimen. The following PK equations can be used to calculate the various kinetic variables.

   Determination of the elimination rate constant:

$$k_e = \frac{\ln \frac{C_1}{C_2}}{\Delta \text{ in time}}$$

   where k_e is the elimination rate constant, C_1 is the measured peak concentration, C_2 is the measured trough concentration, and Δ in time is the elapsed time from C_1 to C_2 in hours.

   Determination of the drug half-life:

$$t_{1/2} = \frac{0.693}{k_e}$$

   where $t_{1/2}$ is the calculated half-life.

Determination of the calculated peak concentration:

$$C_{max} = C_1\,(e^{ke(t)})$$

where C_{max} is the calculated peak concentration and t is the time between the C_1 and the end of the intravenous infusion in hours.

Determination of the calculated trough concentration:

$$C_{min} = C_2\,(e^{-ke(t)})$$

where C_{min} is the calculated trough concentration and t is the time between C_2 and the beginning of the next dose.

Determination of the drug Vd:

$$Vd = \frac{\text{dose}}{t_{inf} \times k_e} \times \frac{(1 - e^{-ke(t_{inf})})}{C_{max} - C_{min} \times e^{-ke(t_{inf})}}$$

where t_{inf} is the duration of the drug infusion.

Determination of the new dosing interval:

$$\tau = \frac{\ln\left(\dfrac{C_{max,desired}}{C_{min,desired}}\right)}{k_e} + t_{inf}$$

where τ (tau) is the new dosing interval, $C_{max,desired}$ is the desired peak concentration for the new dosing regimen, and $C_{min,desired}$ is the desired trough concentration for the new dosing regimen.

Determination of the new dose:

$$\text{dose} = C_{max,desired} \times k_e \times Vd \times t_{inf} \times \frac{(1 - e^{-ke(\tau)})}{(1 - e^{-ke(t_{inf})})}$$

3. One drawback of this method is that it assumes that the PK variables obtained (e.g., vancomycin trough) correlate with PD variables (AUC/MIC). Although this may be true in many cases, some advocate incorporating PD into individualized drug dosing. Alternative methods use PK variables from previous patients (population PK) to estimate the PK in an individual patient. These methods usually require complicated mathematical calculations, many of which are not practical for clinical use. Many software programs are now available for clinician use in patient care that simplify the process of carrying out complex calculations. Bayesian modeling has also been proposed to address the issues posed when using population PK in patient groups that may not be well represented in the population. Using software with population PK variables from non-critically ill patients to interpret or predict PK in critically ill patients could result in errors in designing an appropriate drug-dosing regimen.
4. A position paper provides a more detailed review of the PK, PD, and TDM of commonly used antimicrobials in critically ill patients and notes recommendations that certain antimicrobials should be monitored with TDM (Intensive Care Med 2020;46:1127-53). The aminoglycosides and vancomycin are included on this list because they have routinely been monitored in critically ill patients. The recommendations also include the β-lactam class of antibiotics, linezolid, and the antifungal voriconazole. Finally, the document provides PK and PD target variables for these drugs. The greatest barrier continues to be access to local laboratory analysis and results within a clinically relevant time frame. The reader is referred to the position paper for a more in-depth review.

B. Drug Nomograms/Protocols – A nomogram is a diagram representing the relationship between three or more variables using scales arranged such that one variable can be determined if the other variables are known. A classic drug-dosing example is the once-daily aminoglycoside nomogram (Antimicrob Agents Chemother 1995;39:650-5). The nomogram allows the user to determine only one variable (usually, the dosing interval) using other variables (time from infusion to drug concentration and the measured drug concentration). Many institutions incorporate nomograms into drug-dosing protocols or pathways and routinely refer to them as *drug-dosing nomograms*. Of note, many of these nomograms (e.g., Hartford) were not developed in critically ill patients and likely do not consider the potential for alterations in PK. One of the most commonly used drug-dosing nomograms was developed for continuous infusions of unfractionated heparin. As previously noted, a heparin nomogram can improve time to therapeutic activated partial thromboplastin time when developed specifically for critically ill patients. However, the patient population used to develop a nomogram should be considered because the variables may not apply to all patient populations. An example of this occurs with protocols for insulin infusions in critically ill patients. As previously noted, patients with AKI are at a greater risk of hypoglycemia if treated with an insulin infusion protocol developed in critically ill patients without kidney impairment.

IX. CONCLUSION

There are marked differences in the ways in which critically ill patients respond to drugs. Research in this area has noted significant changes in the PK and PD of certain medications in select critically ill populations. Although these studies have highlighted important issues, considerable work is still needed to better define these changes in different critically ill populations. As research continues to advance, together with our knowledge of how patients respond to drugs differently, critical care clinicians must stay abreast of new information and the ways in which it will affect the care of their patients.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

Increasing the concentration of an antibiotic at an infection site is most important (Answer B is correct). Although case reports describe the use of intraventricular antibiotics in the treatment of meningitis, they have not shown superiority (Answer A is incorrect). Although there is the potential to reduce vancomycin-induced nephrotoxicity, no studies have compared the nephrotoxicity of intraventricular antibiotics with that of intravenous antibiotics, likely because this is not the rationale for their use (Answer C is incorrect). Ototoxicity could also be reduced, but this was not the intent of the locally instilled antibiotics (Answer D is incorrect).

2. **Answer: D**

Three studies have documented an increase in digoxin absorption when the gastric pH is increased, with two studies noting the cause of increased gastric pH from a proton pump inhibitor (Answer D is correct). However, no studies have shown a decreased absorption of carvedilol (Answer A is incorrect), ciprofloxacin (Answer B is incorrect), or diazepam (Answer C is incorrect).

3. **Answer: A**

A decrease in the ionization of a drug allows the drug to pass more easily through membranes. Increasing the ionization would decrease the Vd by decreasing its ability to pass through membranes. A weak acid would be less ionized in a more acidic environment. The patient is likely in diabetic ketoacidosis with a definite acidosis. Ciprofloxacin (a weak acid) is less likely to be ionized and would have an increased Vd (Answer A is correct; Answers B–D are incorrect).

4. **Answer: C**

Levofloxacin has a large Vd. The increase in interstitial fluid volume caused by 6 L of crystalloids would increase the Vd of hydrophilic drugs but would not appreciably affect the Vd of a drug like levofloxacin, which already has a large Vd (Answer C is correct). Tobramycin, daptomycin, and cefepime have relatively small Vd values and are increased in patients with increased interstitial volumes (Answers A, B, and D are incorrect).

5. **Answer: B**

Morphine is a high extraction ratio drug. Mechanical ventilation can decrease cardiac output and thus decrease liver blood flow. The decrease in liver blood flow is inversely proportional to the unbound steady-state concentration. Therefore, it both decreases the hepatic blood flow and increases the unbound concentration (Answer B is correct). The effects of mechanical ventilation on cardiac output would likely decrease oxygen delivery (Answer A is incorrect). Cytokines affect intrinsic clearance but would not affect the concentration of a high extraction ratio drug (Answer C is incorrect). Mechanical ventilation can indirectly affect the unbound concentration (Answer D is incorrect).

6. **Answer: B**

This patient has sepsis, which is associated with an increased production of inflammatory cytokines. These cytokines can decrease the activity of the CYP enzymes and decrease intrinsic clearance. In addition, fluconazole inhibits CYP2C19 activity. Diazepam is a low extraction ratio drug. The hepatic clearance of diazepam is affected by changes in intrinsic clearance (including CYP2C19 activity). The unbound steady-state concentration would be increased, because of a decrease in intrinsic clearance caused by the inflammatory cytokines and CYP2C19 inhibition by fluconazole. The increased unbound steady-state concentrations would cause increased sedation (Answer B is correct). There is no cause for an increase in intrinsic clearance and a corresponding decrease in sedation (Answer A is incorrect). There is no reason for this patient to have a decrease in the unbound fraction of diazepam (Answer C is incorrect). A decrease in albumin could occur with sepsis and would result in an increase in the unbound fraction of diazepam. The increase in unbound fraction would not affect the unbound steady-state concentration, nor would it affect the level of sedation (Answer D is incorrect).

7. **Answer: D**

Under normal conditions, the unbound steady-state concentration for phenytoin is expected to be 10% of the total concentration. Thus, a total concentration of 10-20 mg/L is equivalent to an unbound steady-state concentration of 1-2 mg/L. When the unbound fraction changes, this ratio changes. The unbound steady-state concentration does not change, but the total concentration decreases, which causes the change in the ratio. Using the equations for low extraction ratio drugs (like phenytoin) to explain what has occurred, the unbound fraction is inversely proportional to the total concentration but has no effect on the unbound steady-state concentration (Answer D is correct; Answers A, B, and C are incorrect).

8. **Answer: A**

The kidney plays a role in the excretion and metabolism of insulin. Acute kidney injury will decrease the ability of the kidney to metabolize insulin, which will increase circulating insulin and contribute to hypoglycemia (Answer A is correct). The Vd of insulin in AKI is not well studied and has not been linked with episodes of hypoglycemia (Answer B is incorrect). Hepatic impairment may increase the risk of hypoglycemia with insulin, but an increase in hepatic metabolism is unlikely to affect the risk of hypoglycemia in AKI (Answer C is incorrect). Insulin resistance has been reported in patients with AKI, but this would not contribute to hypoglycemia (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: B**

Decreased anti-Xa activity occurs in critically ill patients receiving several different low-molecular-weight heparins. This patient received the standard fluid bolus and then required more fluid to raise his central venous pressure. This suggests that the patient has redistributed the fluids to the extravascular space. The data showing that edematous patients have lower anti-Xa activity than non-edematous patients supports the connection between anti-Xa activity and absorption (Answer B is correct). Given the patient's fluid distribution, the Vd of enoxaparin would likely be increased, not decreased (Answer A is incorrect). Enoxaparin is not hepatically metabolized (Answer C is incorrect). Although a patient could have an increased anti-Xa activity secondary to decreased renal elimination, this would require a CrCl of less than 30 mL/minute/1.73 m^2. That the patient had a deep venous thrombosis does not correlate with increased activity (Answer D is incorrect).

2. **Answer: C**

Abdominal surgery has been identified as a risk factor for ileus. Antisecretory agents such as pantoprazole alter drug absorption. Traumatic brain injury is significantly associated with intolerance of enteral nutrition, as indicated by increased gastric residuals. This indicates delayed gastric emptying and the risk of altered absorption. Therefore, the combination of abdominal surgery, pantoprazole therapy, and TBI contains the three variables identified in the literature to alter absorption (Answer C is correct). Theoretically, intestinal atrophy could cause changes in absorption, but no data are available to confirm this theory (Answers A and D are incorrect). Changes in cardiac output have been correlated with changes in hepatosplanchnic blood flow. These changes in blood flow are thought to affect absorption, but again, no data have correlated increased cardiac output with increased drug absorption (Answer B is incorrect).

3. **Answer: B**

Propofol is a high extraction ratio drug that is bound to albumin. When the albumin concentration decreases, there is an expected increase in the free fraction of propofol. Using the equations describing the total and unbound concentrations of a high extraction ratio drug, the total concentration is not affected by changes in the free fraction, but unbound concentrations are increased when the free fraction increases (Answer B is correct; Answers A, C, and D are incorrect).

4. **Answer: C**

The update to the KDIGO guidelines notes that the most important factor in determining kidney function is having at least one estimate of GFR. The update recommends that the GFR or the CrCl be estimated to determine this (Answer C is correct). The BUN value can help identify the BUN/SCr ratio indicating intravascular volume contraction and, potentially, a prerenal cause to the patient's AKI, but it does not help in drug dosing (Answer A is incorrect). Total daily urinary output is helpful in diagnosing AKI (oliguric vs. non-oliguric AKI) and in staging AKI (using a urinary output of less than 0.5 mL/kg/hour) but not in drug dosing (Answer B is incorrect). A history of CKD can help determine a baseline kidney function, but the GFR is still needed for changes in drug dosing (Answer D is incorrect).

5. **Answer: C**

The ASHP (American Society of Health-System Pharmacists) vancomycin dosing guidelines recommend a 20- to 35-mg/kg loading dose of vancomycin for serious infections. Given the patient's sepsis, he is likely to have more interstitial fluid, which will increase the Vd of hydrophilic drugs like vancomycin. The 2500-mg dose is near the top end of the recommended 20- to 25-mg/kg loading dose (Answer C is correct). The other doses are outside the recommended 20- to 25-mg/kg loading dose range (Answers A, B, and D are incorrect).

6. **Answer: A**

Critically ill patients younger than 50 are more likely to have augmented renal excretion. Vancomycin is excreted unchanged in the urine. The initial dosing would result in a therapeutic trough concentration, given the increased (augmented) renal excretion of vancomycin. Augmented renal excretion usually returns to normal around day 7. An increased vancomycin trough after a previously therapeutic trough is most likely associated with decreased renal excretion at day 10 of therapy (Answer A is correct). There is no indication that the Vd has changed, which would likely result in lower or unchanged concentrations (Answer B is incorrect). Vancomycin tissue penetration may be better if inflammation is present, but no documented studies correlate decreased inflammation with increased serum concentrations (Answer C is incorrect). The liver does not appreciably metabolize vancomycin, and liver blood flow would not be a factor in the vancomycin concentration (Answer D is incorrect).

7. **Answer: C**

Prospective controlled studies of prolonged piperacillin/tazobactam infusions have shown no improvement in mortality (Answer A is incorrect). No studies have reported neurotoxicity as an outcome (Answers B and D are incorrect). Only retrospective studies have shown improvements in mortality with the use of prolonged or continuous infusions of piperacillin/tazobactam (Answer C is correct).

8. **Answer: C**

Morphine is a high extraction ratio drug. As such, its hepatic metabolism or hepatic clearance depends only on hepatic blood flow. Hepatic clearance equals hepatic blood flow (Answer C is correct). Morphine does not bind to AAG (Answer A is incorrect). Because hepatic blood flow is the main determinant of hepatic metabolism of morphine, changes in protein binding do not affect metabolism (Answer B is incorrect). Changes in intrinsic clearance do not affect the metabolism of morphine as significantly as does hepatic blood flow (Answer D is incorrect).

ACUTE KIDNEY INJURY AND KIDNEY REPLACEMENT THERAPY IN THE CRITICALLY ILL PATIENT

PAIGE GARBER BRADSHAW, PHARM.D., BCCCP

UC HEALTH - UNIVERSITY OF CINCINNATI MEDICAL CENTER
JAMES L. WINKLE COLLEGE OF PHARMACY
CINCINNATI, OHIO

Acute Kidney Injury and Kidney Replacement Therapy in the Critically Ill Patient

Paige Garber Bradshaw, Pharm.D., BCCCP

UC Health - University of Cincinnati Medical Center
James L. Winkle College of Pharmacy
Cincinnati, Ohio

Learning Objectives

1. Define acute kidney injury (AKI).
2. Differentiate between common categories of drug-induced kidney disease.
3. Discuss key principles of continuous kidney replacement therapy (KRT), including indications, timing, and circuit components.
4. Apply drug-dosing concepts in continuous KRT to estimate a sieving coefficient, saturation coefficient, and/or drug clearance on the basis of drug characteristics and device settings.

Abbreviations in This Chapter

AIN	Acute interstitial nephritis
AKD	Acute kidney disease
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARF	Acute renal failure
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
DIKD	Drug-induced kidney disease
EDD	Extended daily dialysis
GFR	Glomerular filtration rate
ICU	Intensive care unit
IHD	Intermittent hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
MW	Molecular weight
RIFLE	Risk, injury, failure, loss, end-stage renal disease
SCr	Serum creatinine
SLED	Sustained low-efficiency dialysis
UOP	Urinary output
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–3 pertain to the following case.
E.R. is a 67-year-old man admitted to your intensive care unit (ICU) several days ago with acute respiratory failure. He required mechanical ventilation and was placed on empiric antibiotics to cover community-acquired pneumonia. His kidney function has worsened over the past 5 days (serum creatinine [SCr] 0.6 mg/dL on admission; today, 2.4 mg/dL), and he now requires kidney replacement therapy (KRT) with continuous venovenous hemofiltration (CVVH). He is extubated, but still unstable. His current medications include as-needed fentanyl, norepinephrine, ceftriaxone, azithromycin, and heparin prophylaxis.

1. Reviewing E.R.'s current medications, which drug-induced kidney disease phenotype is most associated with his antibiotic program?
   A. AKI.
   B. Glomerular disease.
   C. Nephrolithiasis/crystalluria.
   D. Tubular dysfunction.

2. What KDIGO stage best characterizes E.R.'s AKI?
   A. Stage 1.
   B. Stage 2.
   C. Stage 3.
   D. Cannot determine because urinary output (UOP) is not provided.

3. E.R. continues to worsen clinically. He is now febrile with an increasing white blood cell count (WBC). You are asked to dose his antibiotics while he receives CVVH. Which resource would be the best place to begin looking for dosing recommendations?
   A. Intermittent hemodialysis (IHD) guidelines.
   B. Package insert.
   C. Primary literature/dosing summaries.
   D. Estimates using an estimated sieving coefficient.

4. Which best describes the method for solute removal during CVVH?
   A. Convection.
   B. Diffusion.
   C. Both convection and diffusion.
   D. Membrane binding.

5. Which drug would most likely be cleared through a CVVHD circuit?
   A. Drug A: 10% protein bound, 140-Da molecular weight (MW), volume of distribution (Vd) 1.2 L/kg.
   B. Drug B: 90% protein bound, 1030-Da MW, Vd 0.8 L/kg.
   C. Drug C: 40% protein bound, 250-Da MW, Vd 1.5 L/kg.
   D. Drug D: 35% protein bound, 480-Da MW, Vd 4.6 L/kg.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
   Task A: 1, 2, 4
   Task B: 4
2. Domain 2: Therapeutics and Patient Management
   a. Task A: 1, 2, 5, 8
   b. Task B: 3
   c. Task C: 3, 4
3. Domain 3: Professional Practice
   a. Task B: 1, 2, 4, 6

I. ACUTE KIDNEY INJURY

A. Introduction
  1. Acute kidney injury (AKI), previously known as acute renal failure, is an acute decline in kidney function that occurs over hours to days and encompasses the full continuum of kidney injury and functional impairment.
  2. AKI results in the accumulation of waste products and, as urine volume decreases, metabolic disturbances and fluid retention.
  3. AKI has been associated with increased mortality, development of chronic kidney disease (CKD), cardiovascular complications, and end-stage renal disease.
  4. AKI is a heterogeneous syndrome with multiple causes and associated pathophysiologic mechanisms.

B. Epidemiology
  1. The true incidence of AKI varies and depends on the definition used, its cause, and the patient population (e.g., community- or hospital-acquired and severity of illness).
  2. Community-acquired AKI is typically caused by a single disease, including dehydration, sepsis, toxins (bites), and pregnancy. Other causes include HIV infection, hantavirus infection, and malaria or dengue disease. These patients are more often younger and previously healthy and have more difficult access to care.
  3. Hospital-acquired AKI occurs infrequently in patients with less severe illness admitted to a general hospital ward (1.9%–20%). In critically ill patients, the risk is greater, occurring in 20%–67% of patients.
  4. Sepsis and shock are common causes of acute tubular necrosis (ATN), which is a leading phenotype of AKI in critical illness. Other risk factors for AKI include use of intravenous radiocontrast agents, major surgery (especially cardiothoracic), nephrotoxic medications, and chronic medical conditions (e.g., history of CKD, congestive heart failure, and diabetes). Most patients have more than one risk factor.
  5. Mortality rates in patients with AKI are 10%–80%, with the highest in patients with multisystem organ failure (50%) and those requiring kidney replacement therapy (KRT) (up to 80%).
  6. Females tend to be underrepresented in the reported incidence of AKI, accounting for only 40% of cases, which may be related to limited access to healthcare in women or sex-related risks for AKI development in males. Ethnic and racial differences are less well described. A cohort study in the United States found socioeconomic status to account for higher risk of AKI in African American individuals compared with white individuals.

C. AKI Definitions (Table 1)
  1. During the past several decades, many definitions have been used for AKI, making it difficult to compare patient populations across studies. In 2004, the Acute Dialysis Quality Initiative workgroup developed the RIFLE (risk, injury, failure, loss, end-stage renal disease) definition and staging system.
     a. RIFLE categorizes AKI into three grades of increasing severity (risk, injury, and failure) and two clinical outcomes (loss and end-stage).
     b. Staging is based on the degree of SCr increase or a decrease in glomerular filtration rate over 7 days, or the duration of oliguria or anuria.
  2. Because of emerging data suggesting that even small changes in kidney function lead to worse outcomes, in 2007 the Acute Kidney Injury Network (AKIN) criteria was developed.
     a. Similar to RIFLE, this group defined AKI using a staging system of 1-3, defined by a reduction in kidney function over no more than 48 hours using measures of SCr, urinary output (UOP), and need for KRT.

   b. The primary difference between the RIFLE and the AKIN criteria is that AKIN includes a small absolute change in SCr (0.3 mg/dL or more) as part of the diagnostic criteria for AKI and sets a 48-hour time constraint for the criteria to be met. AKIN also omits the outcome classifications (loss and end-stage) previously proposed in the RIFLE criteria.
   c. In patients requiring KRT, AKIN stage 3 is met, regardless of the stage they are in when KRT is initiated.
   d. Several studies have validated these criteria and show that the more severe the RIFLE class or AKIN stage, the worse the clinical outcome.

3. In 2012, a third consensus definition was introduced, the Kidney Disease: Improving Global Outcomes (KDIGO) classification system, which is the current criterion standard.
   a. Separately, the RIFLE criteria and the AKIN criteria were each shown to be suboptimally sensitive for detecting AKI.
   b. The KDIGO criteria combine the strengths of both RIFLE and AKIN, retain the AKIN criteria of a rise in SCr of 0.3 mg/dL within 48 hours, and allow 7 days for a 50% increase in SCr from baseline, as seen in RIFLE.
4. Despite these updates, limitations exist with current definitions.
   a. Current diagnostic markers (SCr and urine output) reflect loss of function rather than damage or injury.
   b. SCr is an imperfect biomarker for estimation of glomerular filtration rate and is significantly affected by muscle mass. In the critically ill, production may be decreased and volume of distribution may be affected by volume overload, both decreasing SCr levels.
   c. Baseline SCr values may not be available in all patients. Various techniques may be used such as admission SCr, inpatient nadir SCr, imputed creatinine using estimated glomerular filtration rate (eGFR) 75 mL/min/1.73m2, or preadmission baseline, all with certain strengths and limitations.
   d. Decreased urine output is a physiologic response to intravascular volume depletion and may not imply tubule injury. It is also confounded by use of diuretics.
   e. Current consensus definitions do not address the subphenotypes of AKI, which may support future development of therapeutics or trial enrichment for management of AKI.

Table 1. Criteria for Establishing AKI

RIFLE		AKIN		KDIGO		All Three Classification Systems
Stage	**SCr/GFR Criteria**	**Stage**	**SCr Criteria**	**Stage**	**SCr Criteria**	**UOP Criteria**
R	Increase to ≥ 1.5-fold or GFR decrease > 25% from baseline	**1**	Increase to 1.5- to 2-fold above baseline or by ≥ 0.3 mg/dL within 48 hr	**1**	Increase to 1.5- to < 2-fold above baseline over 7 days or by ≥ 0.3 mg/dL within 48 hr	< 0.5 mL/kg/hr for 6-12 hr
I	Increase to ≥ 2-fold or GFR decrease > 50% from baseline	**2**	Increase to ≥ 2- to 3-fold above baseline	**2**	Increase to ≥ 2- to < 3-fold above baseline	< 0.5 mL/kg/hr for ≥ 12 hr
F	Increase to ≥ 3-fold, GFR decrease > 75% from baseline, or SCr ≥ 4 mg/dL (acute increase of at least 0.5 mg/dL)	**3**	Increase > 3-fold above baseline or ≥ 4 mg/dL with an acute rise of ≥ 0.5 mg/dL or on KRT	**3**	Increase ≥ 3-fold above baseline or ≥ 4 mg/dL or initiation of KRT	< 0.3 mL/kg/hr for ≥ 24 hr or anuria for ≥ 12 hr

Table 1. Criteria for Establishing AKI (*continued*)

RIFLE		AKIN		KDIGO		All Three Classification Systems
Stage	**SCr/GFR Criteria**	**Stage**	**SCr Criteria**	**Stage**	**SCr Criteria**	**UOP Criteria**
L	Complete loss of function for > 4 wk					
E	Complete loss of function for > 3 mo					

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; KRT = kidney replacement therapy; RIFLE = risk (R), injury (I), failure (F), loss (L), end-stage kidney disease (E); SCr = serum creatinine; UOP = urinary output.

5. Kidney dysfunction/damage is a spectrum.
    a. In 2012, KDIGO proposed four categories to encompass the spectrum of kidney function (Figure 1; Table 2 provides detailed definitions).
        i. No known kidney disease (NKD)
        ii. AKI: Acute kidney dysfunction over 7 days or less
        iii. Acute kidney disease (AKD): For those who meet the AKI definition or with other types of kidney dysfunction/damage for less than 3 months
        iv. Chronic kidney disease (CKD): Kidney dysfunction/damage for more than 3 months
    b. The definitions were intended to improve consistency in applied nomenclature in care, research, and public health and to identify patients with AKD who may need therapy to restore kidney function and mitigate or reverse kidney damage.
    c. The definition of AKI recovery is not well defined; however, identification of early resolution within days versus delayed resolution of weeks to months, has important prognostic implications. Nonresolving AKI is associated with greater risk of major adverse kidney events, specifically the development of chronic kidney disease.
    d. Increasingly, patients in the AKD subgroup are targeted for interventions designed to prevent CKD development, including bundled strategies delivered in AKI follow-up clinics. Interprofessional survivor clinics for AKI are reported to improve patient education, engagement, follow-up, and outcomes. Pharmacists can play a central role in such initiatives by providing a careful medication evaluation (renally eliminated and nephrotoxic drugs), monitoring and supportive care for key concurrent conditions (e.g., hypertension, lipid management), and patient and caregiver education.

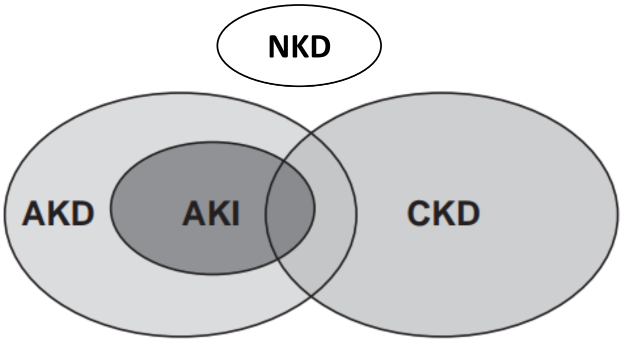

Figure 1. Overview of the spectrum of kidney disease.

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; NKD, no known kidney disease.

Table 2. KDIGO's Definitions of NKD, AKI, AKD, and CKD According to Function and Structure

	Functional Criteria (change in SCr, GFR,[a] or UOP)	**Structural Criteria (damage[b] or no damage and duration)**
NKD	GFR ≥ 60 mL/min/1.73 m^2, stable SCr	No damage
AKI	Increase in SCr by 50% within 7 days Or Increase in SCr by 0.3 mg/dL within 2 days Or Oliguria	No criteria
AKD	AKI Or GFR < 60 mL/min/1.73 m^2 for < 3 mo Or Decrease in GFR by ≥ 35% or increase in SCr by > 50% for < 3 mo	Kidney damage for < 3 mo
CKD	GFR < 60 mL/min/1.73 m^2 for > 3 mo	Kidney damage for > 3 mo

[a] Assessed from measured or estimated GFR.

[b] Kidney damage is assessed by pathology, biomarkers (urine or blood), imaging, and kidney transplantation (for CKD).

AKD = acute kidney disease and disorders; CKD = chronic kidney disease.

D. Diagnostic Workup and Evaluation
    1. There is no single specific test for accurately diagnosing AKI.
    2. A thorough history and complete examination should be completed, including rate of kidney function decline, associated symptoms, and coexisting diseases.
    3. A comprehensive review of current and recent medications should be conducted. Drug-related injury is a leading cause of AKI.
    4. Chemistries (blood urea nitrogen [BUN], SCr, serum electrolytes, albumin, and a complete blood cell count) and a urinary analysis (microscopy, sodium, and osmolality) may assist in determining the type of failure (e.g., prerenal, intrinsic, postrenal).
    5. Bladder catheterization is reasonable in most cases to augment diagnostic accuracy. Compelling indications for catheterization include cases in which ins and outs are difficult to measure accurately, such as in patients with incontinence or those with evident postvoid residuals. If a catheter is present without UOP, it should be evaluated for patency.
    6. Abdominal compartment syndrome should be ruled out if clinically suspected. Acute oliguria and AKI can be the result of increasing renal outflow pressure and reduced kidney perfusion.
    7. Routine use of kidney ultrasonography is of limited usefulness because most ICU-related AKI is associated with decreased effective arterial blood volume and/or ATN. However, it may be useful in high-risk patients or after an initial evaluation fails to reveal the cause of AKI.
    8. Renal biopsies have limited usefulness but may be necessary. They are most useful in intrinsic renal failure not associated with ATN or when glomerulopathy is suspected.
    9. The "furosemide stress test" has been used as a tool to predict AKI progression. Tubular dysfunction after AKI may affect diuretic response from loss of sodium transporter expression, Na-K-ATPase redistribution and organic acid transporter mistargeting. A dose of 1 mg/kg in patients who are diuretic naive and 1.5 mg/kg in patients who are non-diuretic naive is typically used. UOP thresholds vary across studies, but response is most commonly defined as 200 mL over 2 hours and predicts higher likelihood of tubular function recovery.

10. Biomarkers: Recently, significant advances were made in the field of biomarkers for predicting and detecting AKI (Figure 2). When the KDIGO guidelines were released in 2012, these data were not available; thus, they were not included in the criteria for the diagnosis of AKI. Despite emerging literature and calls for revision of AKI classification to incorporate biomarkers, the most recent 2019 KDIGO controversies conference on AKI suggests that additional research is needed before including these biomarkers in the diagnostic criteria for AKI.

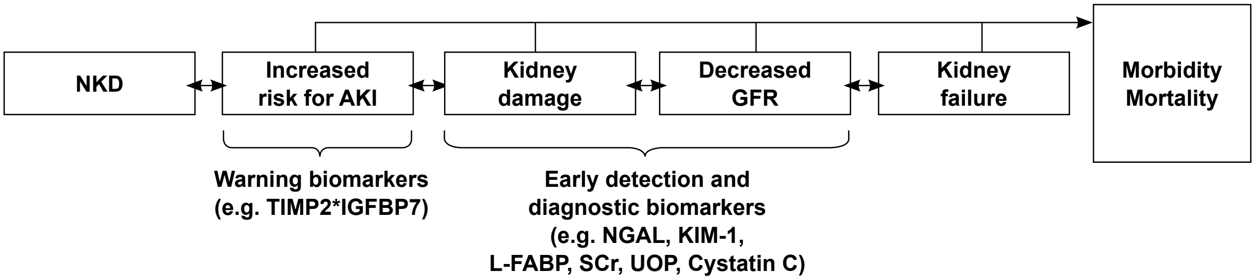
NKD
Increased risk for AKI
Kidney damage
Decreased GFR
Kidney failure
Morbidity Mortality
Warning biomarkers (e.g. TIMP2*IGFBP7)
Early detection and diagnostic biomarkers (e.g. NGAL, KIM-1, L-FABP, SCr, UOP, Cystatin C)

Figure 2. Evolution of AKI as it corresponds to biomarker release.

Adapted from: Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet 2012;380:756-66.

a. Functional markers: Indicate the kidney's capacity for clearance and are used to estimate GFR and functional loss; these can help indicate a need for drug dosing changes
   i. Examples: SCr, UOP, serum cystatin C, proenkephalin, beta-trace protein, β2 microglobulin
   ii. These biomarkers may rise with or without evidence of structural damage to the kidney (e.g., prerenal AKI, which could correspond to a reduced GFR that may not yet have resulted in kidney damage).
   iii. Recent evidence suggests that cystatin C can predict the pharmacokinetics of medications as well as, if not better than, SCr with certain renally eliminated medications. Drug-specific dosing models need to be developed and tested.
      (a) Antimicrobials have been the most commonly studied drug class investigating the association between cystatin C, corresponding eGFR, and predicted drug clearance. Specific medications that have been evaluated using cystatin C prediction of pharmacokinetics include vancomycin, aminoglycosides, β-lactams, tenofovir, digoxin, dabigatran, and carboplatin.
b. Damage/injury markers: Signal injury to the kidney cells or at least cellular distress; these can help identify patients who would benefit from limiting exposure to nephrotoxins
   i. Warning biomarkers (e.g., cell-cycle arrest markers [TIMP-2•IGFBP7])
      (a) TIMP-2•IGFBP7 is a U.S. Food and Drug Administration–approved urinary test; these biomarkers are released during a pause (an "arrest") in mitosis when the biomarker indicates the cell may be injured and should not divide.
      (b) In the PrevAKI (Intensive Care Med 2017;43:1551-61) and BigpAK (Ann Surg 2018;267:1013-20) trials, surgical patients with a high risk of AKI on the basis of [TIMP-2•IGFBP7] greater than 0.3 who were randomized to an AKI prevention bundle had a lower incidence of AKI than did individuals who received usual care. This is a significant advancement because it suggests that even in high-risk patients, AKI can be prevented.

(c) A retrospective cohort study of the ProCESS trial by the ProGReSS-AKI investigators (JAMA Netw Open 2022:5:e2212709) evaluated the incorporation of TIMP-2•IGFBP7 assessment (TIMP-2•IGFBP7 greater than 2.0) into the classification of AKI as well as the association with survival among patients with septic shock and similar AKI stage classification. In patients with existing AKI, a positive biomarker was associated with lower survival and higher mortality at 30 days. These data suggest that incorporation of cell-cycle arrest biomarkers may augment AKI staging in patients who meet functional criteria for AKI.

ii. Early detection and diagnostic biomarkers (e.g., NGAL, KIM-1, L-FABP, NAG, urine cystatin C, CCL14) have been studied as early indicators of kidney damage or predictors of persistent AKI; each test has different performance characteristics

iii. The cost-effectiveness of using these biomarkers to inform routine care has not been well studied. Because of the high costs associated with the management of AKI, particularly when dialysis is required, a systematic approach to biomarker use could prove economical. Additional research is needed to explore this further.

c. Although the evidence is promising, novel biomarker use is not yet mainstream. Several factors, including limited evidence, implementation challenges, and cost, have precluded widespread adoption as an adjunct to SCr and UOP at this time. As use continues, additional information on the logistics of successfully applying these tests is expected.

11. Kinetic eGFR is another strategy that has been proposed to evaluate rapidly changing kidney function (J Am Soc Nephrol 2013;24:877-88). Creatinine is a lagging marker of kidney function and may take 48 hours to increase from the onset of kidney damage. The kinetic eGFR equation is thought to provide a quantitative solution to estimate kidney function in this difficult scenario. Using a simple algebraic formula, including the initial creatinine content, the volume of distribution, the creatinine production rate, and the change in SCr over time, inputs can be used to quantitatively interpret creatinine change. Kinetic eGFR predicted AKI and the need for KRT more accurately than Modification of Diet in Renal Disease (Clin Kidney J 2017;10:202-8). Published literature on the use of kinetic eGFR to inform medication dosing remains in infancy.

E. Causes and Mechanisms of AKI

1. Prerenal: AKI attributable to decreased kidney perfusion. Decreased kidney perfusion could be caused by low effective arterial blood volume, as in hypovolemia or acute decompensated heart failure, peripheral vasodilation, or renal vasoconstriction or renal occlusion. Some have suggested to do away with the nomenclature “prerenal” because it could be misinterpreted to mean hypovolemia, which only reflects a small subset of cases associated with decreased kidney perfusion.
2. Renal (intrinsic): AKI secondary to parenchymal or vascular diseases. ATN is the most commonly cited example of this category of AKI in the hospital setting. AKI secondary to vasculitis, glomerulonephritis, interstitial nephritis, infections, connective tissue disease, and crystalluria are in this category as well.
3. Postrenal: AKI associated with urinary tract obstruction. Common causes include prostatic hypertrophy, nephrolithiasis, and tumor obstruction. If an obstruction is suspected, placing a urinary catheter may be a sufficient temporizing measure. If higher in the urinary tract, nephrostomy tubes may be warranted to alleviate hydronephrosis.

F. Drug-Induced Kidney Disease (DIKD)
  1. Drugs are associated with about one-third of AKI cases in the hospital. The concept of “nephrotoxin stewardship” has been proposed. *Nephrotoxin stewardship* is a term taken from antimicrobial stewardship that generally refers to “coordinated interventions to improve and measure the appropriate use of drugs by promoting the selection of the optimal drug regimen, including dosing, duration of therapy, and route of administration” (Clin Infect Dis 2016;62:e51-77). Kane-Gill has proposed 3 goals for nephrotoxin stewardship—medication safety, kidney health, and avoidance of unnecessary costs—with recommended strategies associated with each goal (Crit Care Clin 2021;37:303-20).
  2. A standardized classification system (Kidney Int 2015;88:226-34) was proposed for DIKD that classifies kidney dysfunction according to three primary factors:
     a. Phenotype of kidney injury: AKI (ATN, acute interstitial nephritis [AIN], osmotic nephrosis), glomerular disorder (hematuria, proteinuria), nephrolithiasis (crystalluria, nephrolithasis, obstruction), and tubular dysfunction (renal tubular acidosis, Fanconi syndrome, syndrome of inappropriate diuretic hormone, diabetes insipidus, phosphate wasting)
     b. Mechanism: Type A (dose-dependent toxicities), type B (unpredictable, not dose-dependent)
     c. Time course: Acute (1–7 days), subacute (8–90 days), chronic (more than 90 days)
  3. More recently, a group of experts proposed a more contemporary DIKD schema that incorporates functional changes and tissue damage biomarkers (Crit Care 2023;27:435). The four categories include: “dysfunction without damage”, “damage without dysfunction”, “both dysfunction and damage,” and “neither dysfunction nor damage”.
  4. Extrarenal: Drugs that alter renal perfusion or influence intraglomerular hemodynamics can heighten a patient’s risk of AKI. Examples include the following:
     a. Loop diuretics: Intravascular volume depletion leading to loss of effective arterial blood volume
     b. Negative inotropes or vasodilatory antihypertensives that reduce renal perfusion
     c. Nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs)
        i. Normally, glomerular pressure is maintained, in part, by vasodilation of the afferent arterioles or vasoconstriction of the efferent arterioles.
        ii. Vasodilation of the afferent arteriole is partly controlled by the effects of prostaglandins. Medications that decrease prostaglandin synthesis such as NSAIDs decrease the ability of the afferent arteriole to vasodilate and thus increase the risk.
        iii. Vasoconstriction of the efferent arteriole, which helps maintain transcapillary pressure, is mediated through angiotensin II. Drugs that block angiotensin II such as ACEIs and ARBs prevent effective efferent vasoconstriction and thus increase the risk.
        iv. The so-called “triple whammy” of NSAIDs/diuretics/ACEIs or ARBs has been described as having a uniquely high risk of AKI because of the multiplicity of the intraglomerular hemodynamic impact (BMJ 2013;346:e8525). Information from an adverse drug event report database showed that the median time to AKI onset was 20 days with a single triple whammy drug, 44 days for two drugs, and 8 days for three drugs. The onset of AKI is generally early and decreases over time, especially if an NSAID is part of the combination therapy (Plos One 2022;17:e0263682).
        v. Use of calcineurin inhibitors, particularly in the setting of other risk factors for AKI, is thought to interfere with renal hemodynamics.

5. Intrarenal toxicity: There are several types of kidney toxicity from xenobiotics. These include direct tubular toxicity, AIN, glomerular diseases, osmotic nephrosis, crystalluria/nephrolithiasis, and altered electrolyte handling.
    a. Direct tubular toxicity: Drugs can be associated with direct tubular damage, cell apoptosis, and necrosis. ATN may be suggested by the presence of granular casts (“muddy brown casts”) or renal tubular epithelial cells on a urinalysis.
        i. Examples of drugs that contribute to ATN: Intravenous contrast, aminoglycosides, amphotericin B, vancomycin, colistin, antiviral agents, platinum chemotherapy
        ii. Direct tubular toxicity is often a type A injury that responds to dose adjustment or drug discontinuation and supportive care.
    b. AIN: Drug-associated AIN is thought to be a cell-mediated immune response, analogous to a type 4 hypersensitivity reaction. Microscopic hematuria, sterile pyuria, and nonnephrotic range proteinuria are features of AIN on urinalysis. Other features of AIN can include urine and/or peripheral eosinophilia with clinical symptoms of fever, rash, and joint pains. Although commonly cited in the literature, these may not be universally present; in fact, only 10%–30% of patients with this diagnosis have the “classic triad” of eosinophilia, fever, and rash. A kidney biopsy can be considered but, in the acute setting, is rarely performed until other causes are ruled out.
        i. Drug causes have been implicated in up to 75% of AIN cases. Other separate or concurrent contributors to AIN include infections (5%–10%), idiopathic causes (5%–10%), and causes associated with systemic diseases (10%–15%).
        ii. Examples of drugs that contribute to AIN: Penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, NSAIDs and cyclooxygenase-2 [COX-2] inhibitors, proton pump inhibitors, immune checkpoint inhibitors, phenytoin, valproic acid, ranitidine, diuretics, and cocaine
        iii. Management of AIN includes discontinuation of the offending agent. These injuries are often subacute and take weeks to months to resolve. Steroids may be used, but this remains controversial.
        iv. Recently, the combination of piperacillin/tazobactam and vancomycin received specific attention for its risk of nephrotoxicity. In ICU patients, observational studies suggest that empiric courses of less than 72 hours are no more nephrotoxic than other such combinations. Preclinical models in rats using histopathology and novel urinary kidney biomarkers suggest no evidence of heightened risk with the combination (J Antimicrob Chemother 2020;75:1228-36). In addition, a prospective cohort study (Intensive Care Med 2022;48:1144-55) identified an increased risk of creatinine-defined AKI with piperacillin/tazobactam and vancomycin combination compared with the cefepime and vancomycin combination, but not changes in cystatin C, blood urea nitrogen, mortality, or need for KRT. This finding supports the idea that the piperacillin/tazobactam and vancomycin effects on creatinine may represent a pseudo-toxicity rather than true AKI. In observational data in humans, evidence still favors a potential increased risk of AKI with the combination and remains an ongoing area of research; thus, the risk-benefit of other combinations should be considered in conjunction with other potential toxicities or antibiotic stewardship efforts.
    c. Glomerular diseases: DIKD rarely manifests as glomerular disease. Glomerular diseases from medication can include immune-mediated glomerular diseases, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with necrotizing and crescentic/pauci-immune glomerulonephritis, drug-induced lupus, and drug-associated membranous nephropathy. In addition, drugs may cause direct glomerular toxicity, resulting in minimal change disease or focal segmental glomerulosclerosis. Depending on the type of injury, suggestive diagnostics of drug-associated glomerular diseases may include proteinuria, hematuria, positive antibody tests, rash, fever, myalgias, and polyarthritis. A kidney biopsy is often pursued.

        i. Examples of drugs that contribute to immune-mediated glomerular diseases include hydralazine and propylthiouracil. Drugs that contribute to direct glomerular cell toxicity include lithium, NSAIDs, sirolimus, anabolic steroids, anti-angiogenesis drugs (i.e., bevacizumab, sunitinib, sorafenib), chemotherapeutics (i.e., mitomycin C, gemcitabine), calcineurin inhibitors, interferon, thienopyridines (i.e., clopidogrel, prasugrel), and quinine.
        ii. Management of drug-induced glomerular disease includes identifying the subtype and discontinuing the offending agent. These injuries are often type B reactions, subacute or chronic, and may partly be irreversible. Immunosuppressants and plasmapheresis may be indicated for treatment.
    d. Osmotic nephrosis: Drugs such as mannitol; hydroxyethylstarch; immunoglobulins, especially those containing sucrose; and dextrans may lead to osmotic nephrosis. In these cases, drug molecules undergo pinocytosis and cellular accumulation, and the cells become swollen and vacuolated, leading to tubular lumen obstruction.
    e. Crystalluria/nephrolithiasis: Certain medications are insoluble in the urine and can result in crystalline nephropathy and/or kidney stones. Suggestive diagnostics include crystalluria on urinary analysis, overt nephrolithiasis, and ultrasound findings indicative of obstruction. Examples of drug culprits include antibiotics, acyclovir, methotrexate, antiretrovirals, triamterene, and ethylene glycol–associated calcium oxalate crystal precipitation.
    f. Altered electrolyte handling/tubular dysfunction: Drugs may alter how the kidney handles electrolytes, tubular proteins, and water. Example patterns include the syndrome of inappropriate antidiuretic hormone, an acquired Fanconi syndrome; renal tubular acidosis; and nephrogenic diabetes insipidus. Serum and urine electrolyte abnormalities, altered serum and urine osmolality, and an altered acid-base profile may each indicate this type of DIKD. Examples of drug causes include antiretrovirals, lithium, selective serotonin reuptake inhibitors, antiepileptics, and vincristine.
6. A comprehensive medication list, titled the “Acute Kidney Intervention and Pharmacotherapy (AKIP)” list, was recently established and includes 681 unique drugs or drug combinations that are renally dosed, potentially nephrotoxic, or both in the acutely ill population (*Ann Pharmacother.* 2025;59(4):371-377). This evidence-based, standardized list of medications will be useful to harmonize future epidemiologic studies and medication quality improvement initiatives.

G. AKI Survivorship
    1. Recently, increased emphasis has been placed on AKI survivor care. AKI survivor care focuses on patients with an episode of AKI during hospitalization who are being discharged. Individuals have tried specific AKI survivor clinics to improve comprehensive kidney care follow-up to limit the burden of CKD.
    2. The landmark FUSION randomized controlled trial (*Clin J Am Soc Nephrol.* 2021;16:1005-14) enrolled patients who survived an episode of stage 2 or 3 AKI and randomized them to either early nephrology follow-up with a bundled care intervention or usual care. Although process outcomes were improved with bundled care (increased nephrology visits, kidney function monitoring, medication reconciliation completion and review), clinical outcomes, including a major acute kidney event at 1 year, were no different. More research is needed to determine the optimal method for follow-up in AKI survivors that is aligned with best practices and patient-centeredness.

Patient Case

Questions 1–3 pertain to the following case.
F.B. is a 68-year-old male patient (weight 70 kg) admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, diabetes, and hypertension. He takes both enalapril and glipizide once daily, as well as acetaminophen as needed. Before this admission, he had otherwise been healthy. He saw his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his hemoglobin A1C was 5.2%. His laboratory workup was also unremarkable: WBC 5.0 x 10^3 cells/mm^3, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24 x 10^3 cells/mm^3, BUN is 38 mg/dL, and SCr is 3.2 mg/dL, with 325 mL of UOP since his admission 24 hours ago.

1. Which best describes F.B.'s AKI?
   A. RIFLE class R.
   B. AKIN stage 1.
   C. RIFLE class F or AKIN stage 3.
   D. RIFLE class E or AKIN stage 3.

2. Which medication is most likely contributing to his AKI?
   A. Enalapril.
   B. Glipizide.
   C. Acetaminophen.
   D. Both enalaparil and glipizide equally.

3. When evaluating F.B.'s potential causes of AKI, which additional information or test would be most important to consider or obtain?
   A. Rate of loss, symptoms, and coexisting diseases and medications.
   B. Renal evaluation using ultrasonography because this can determine the cause of AKI in most patients.
   C. Review of blood chemistries because this will likely determine the cause of injury.
   D. Renal evaluation using biopsy.

II. KIDNEY REPLACEMENT THERAPIES

A. General Approaches to Managing AKI
   1. Once injury has occurred, therapy consists of providing supportive care and limiting additional insults, including nephrotoxin exposure.
   2. In patients with shock, adequate fluid resuscitation should be initiated to restore effective circulation without producing volume overload.
   3. No specific pharmacologic therapy is effective in treating or reversing AKI.
   4. Metabolic derangements and volume status should be followed closely, and KRT should be initiated when other approaches have failed.

5. Historically, KRT has been offered when a patient fulfills at least one of the AEIOUs: severe Acidosis, Electrolyte abnormalities (eg, hyperkalemia), Intoxication), refractory volume Overload, or symptomatic Uremia. The multicenter BICAR-ICU study showed that randomization to sodium bicarbonate administration for a pH of 7.2 or less and PCO2 of 45 mm Hg or less, rather than no therapy, failed to improve all-cause mortality or death in ICU patients. However, of note, patients in the bicarbonate group had a significantly lower rate of new dialysis initiation, suggesting this temporizing measure had a secondary benefit and decreased dialysis initiation for acidemia or hyperkalemia while kidneys spontaneously improved.
6. No consensus exists on the optimal timing of KRT. It is unclear whether KRT should be initiated when a patient reaches KDIGO stage III or potentially earlier to avoid complications associated with metabolic/fluid derangements. Several recent randomized controlled trials regarding KRT timing have been published with disparate results. These include the ELAIN and AKIKI trials published in 2016, the IDEAL-ICU trial published in 2018, and the STARRT-AKI trial published in 2020.
    a. STARRT-AKI: Multicenter, multinational trial of 2927 individuals with stage 2 or 3 AKI who received either "accelerated KRT," meaning therapy was initiated within 12 hours of meeting eligibility criteria, or "standard KRT," meaning therapy was not initiated unless the patient fulfilled a conventional indication (analogous to the AEIOU indications mentioned earlier). Clinicians needed to attest to equipoise in the decision to initiate KRT before the patient could be enrolled. For the primary end point of all-cause mortality at 90 days, there was no difference between groups (44% in each group). Only two-thirds of the patients in the standard KRT group ultimately required dialysis, whereas 97% of the patients in the accelerated KRT group received dialysis. There were more adverse events in the accelerated KRT group.
    b. At this point, although the findings of these trials somewhat vary, it appears that there is no consistent, reproducible advantage to beginning KRT early in a patient's course as opposed to waiting until stage 3 AKI with an urgent indication.
7. The practice of KRT discontinuation is non-standardized but typically occurs when the precipitant is improved or resolved (e.g., sepsis controlled) and patients can satisfactorily maintain their fluid and solute balance without extracorporeal support.

B. Renal Replacement for AKI
1. Modalities are classified according to duration as intermittent KRT, prolonged intermittent KRT, or continuous KRT.
2. A defining feature of the type of KRT is the mechanism of solute and water transport through a semipermeable membrane by convection, diffusion, or both.
    a. Convection uses the concept of "solute drag" and can remove both small- (less than 500-1000 Da) and middle- (less than 10,000 Da) molecular-weight solutes. Solute removal occurs when the transmembrane pressure drives water and solute across a semipermeable membrane. This process involves adding replacement fluid (pre- and/or post-filter) to replace the excess volume that is being removed and replenish the desired electrolytes. Pre-filter replacement fluid may improve filter life and deter circuit clotting. Post-filter replacement fluid may improve solute clearance efficiency because of the hemoconcentration of blood entering the dialyzer.
    b. Diffusion is the movement of solutes from an area of higher solute concentration to an area of lower concentration. A concentration gradient is produced by running an electrolyte solution (i.e., dialysate fluid with a flow rate of 17–40 mL/minute) countercurrent to the flow of blood. Small-molecular-weight solutes (less than 500 Da) are cleared efficiently.

C. Intermittent Hemodialysis (IHD)

1. IHD is the most common form of KRT used in the acute setting for treating patients with AKI or end-stage renal disease needing dialysis.
2. Rapid metabolic clearance and/or fluid removal occurs over about 3- to 4-hour sessions.
   a. Intradialytic hypotension occurs in up to 30% of patients, which can lead to early dialysis termination or compromise of residual renal function. Several strategies to improve hemodynamics during IHD have been suggested, including fluid administration, ultrafiltration and sodium modeling, periprocedural antihypertensive hold, and midodrine or vasopressor therapy. Selection among these options is patient-specific and should only be done in conjunction with a careful evaluation of underlying etiologies for hypotension, including potential infection and cardiac dysfunction.
   b. Patients with preexisting hypotension before IHD (e.g., septic shock), may not tolerate the large fluid and electrolyte shifts during IHD resulting in further hemodynamic alterations.
   c. In patients with head trauma or hepatic encephalopathy, hypotension can reduce cerebral perfusion. Changes in solute concentrations can also worsen cerebral edema. Rapid plasma clearance of solutes acutely decreases their systemic intravascular concentrations while intracranial concentrations remain unchanged. This relatively high intracranial concentration of solute results in water transport back across the blood-brain barrier, which contributes to cell swelling, cerebral edema, and increased intracranial pressure. Careful consideration of IHD use in these populations is warranted.

D. Continuous KRT

1. Continuous KRT is the most commonly used modality of KRT in hemodynamically unstable ICU patients. Past nomenclature of continuous KRT is continuous renal replacement therapy (CRRT) and may still be referred to as such in clinical practice or in historical literature.
2. Continuous KRT modalities include continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF).
3. SCUF, or slow continuous ultrafiltration, is another type of continuous KRT that removes fluid without the need for replacement solutions. This therapy has limited effect on removal of waste products (e.g., BUN) or electrolytes and cannot correct acid-base abnormalities.
   a. Solute clearance during CVVH occurs by convection, and the ultrafiltration rate determines the clearance rate for most solutes.
   b. Solute clearance during CVVHD occurs by diffusion.
   c. For CVVHDF, solute removal occurs by both convection and diffusion, with diffusion commonly the dominant waste removal modality.
4. Because of the continuous nature of continuous KRT and prolonged exposure of blood to foreign surfaces of the extracorporeal circuit, anticoagulation is often required to prevent circuit clotting, maintain membrane permeability, and prevent blood loss in the clotted filter. Unfractionated heparin and regional citrate anticoagulation (RCA) are the most common anticoagulant options. Compared with systemic unfractionated heparin, RCA has been shown to increase filter life span and decrease bleeding, but with no difference in mortality. Challenges associated with RCA include accumulation in patients with reduced liver function and shock states, metabolic complications (acidosis, alkalosis, hypernatremia, hypocalcemia, and hypercalcemia), increased complexity, and need for use of a strict protocol. Systemic unfractionated heparin infusion remains an option for anticoagulation when unable to administer RCA. The recommended dose and monitoring is variable; however, it may be reasonable to titrate to a target activated partial thromboplastin time of 45–60 seconds or anti-Xa activity of 0.3–0.6 IU/mL. Heparin may also be administered regionally via infusion into the arterial line of the circuit with administration of continuous protamine post-filter to inactivate the unfractionated heparin.

E. Prolonged Intermittent KRT
   1. Sustained low-efficiency dialysis (SLED), sustained low-efficiency daily diafiltration (SLEDD-f), extended daily dialysis (EDD), and accelerated veno-venous hemofiltration are all referred to as prolonged intermittent renal replacement therapy and are considered hybrid modalities between intermittent and continuous options.
   2. Prolonged intermittent KRT is typically delivered using conventional hemodialysis machines with low blood-pump speeds (around 200 mL/min) and low dialysate flow rates (around 300 mL/min) for extended periods: 6 to 12 hours per day versus 3 to 4 hours for IHD or 24 hours for continuous KRT.
   3. Similar to continuous KRT, they allow for improved hemodynamic stability by producing gradual solute and volume removal compared with IHD.
   4. These therapies have certain advantages over continuous KRT. They produce high solute clearances, use existing IHD machines, eliminate the need for external solutions, and allow “time away” when various diagnostic and therapeutic procedures are needed, liberating health care workers from continuous involvement with the circuit. Disadvantages include limited data on drug clearance and a period in which solute and fluid management is paused (when off circuit).

F. Choosing a Mode
   1. Data are conflicting regarding the renal replacement mode of choice for critically ill patients.
   2. Outcomes such as mortality and renal recovery appear to be no different between IHD and continuous KRT; however, most studies are limited by design, patient characteristics, and crossover between different modalities.

G. Continuous KRT and Drug-Dosing Concepts
   1. Drug dosing during continuous KRT and SLED is often unclear because this information is not included in package inserts. Manufacturers are not required to study how these therapies alter clearance. General dosing considerations for continuous KRT include:
      a. For most medications, loading doses require no adjustment.
      b. If a drug is normally cleared by the kidneys or is removed by other KRT modalities, continuous KRT may significantly affect its removal.
      c. When available, drug-specific literature should be used to determine dose and frequency to minimize the likelihood of dosing errors. Continuous KRT may be interrupted for various reasons, and if held for an extended time or beyond scheduled medication dosing frequencies, medication dose adjustments may be required.
      d. Use caution when extrapolating historical literature to modern practice because current dialyzers can more readily clear small and middle MW molecules, and flow rates are higher than previously used. Collectively, these aspects would be expected to increase drug clearance and make historically recommended doses insufficient when applied to modern practice.
      e. With the many variables associated with continuous KRT delivery (e.g., modality, dialyzers, circuit downtime, patient instability), therapeutic drug monitoring should be used, when available, especially for drugs with a narrow therapeutic index.
   2. KRT modality, dialysis dose (e.g., more frequent IHD, higher dialysis dose/effluent flow rate increase drug elimination), and drug properties influence medication elimination. Effluent is any fluid leaving the circuit and not returned to the patient. This is spent fluid and could be dialysate or an ultrafiltrate from the blood.
   3. Drug proprieties that influence removal during continuous KRT include protein binding, molecular weight (MW), and volume of distribution (Vd). Drug charge (Gibbs-Donnan effect) is less important.
      a. The ability of a drug to bind to plasma protein (i.e., albumin) greatly influences how it is removed by continuous KRT. Removal is inversely proportional to the percent bound (i.e., the higher the percent bound, the less removed). Protein binding affects removal for both convection and diffusion.

b. Solutes are considered to have a small MW (less than 1000 Da), middle MW (1000-30,000 Da), or large MW (greater than 30,000 Da). Most unbound drugs have an MW less than 500 Da (e.g., cefepime = 480 Da). Diffusive clearance (as with IHD and CVVHD) readily removes small MW drugs to a greater extent than middle MW drugs, whereas convective clearance modalities (as with CVVH) remove both small and middle MW drugs well. Highly protein bound drugs, as with albumin binding (67,000 Da), appear to have a high MW because of the association with the plasma protein. This large size would exceed the typical pore size of a high-flux, high-efficiency dialyzer, which is standard of care, and lead to reduced drug clearance.

c. Vd is inversely related to extracorporeal removal, wherein a larger Vd decreases elimination through the circuit because the drug is distributed throughout the body compartments. For continuous KRT, the slower rates allow for steady redistribution between body compartments, which can facilitate removal of drugs with a larger Vd to a greater degree than with IHD. Medications are generally considered to have a large Vd when greater than 1 L/kg and a small Vd when less than 0.3 L/kg.

4. Continuous KRT modalities and their influence during therapy
   a. CVVH
      i. Solute removal during CVVH is by convection. Convection is influenced by the membrane pore size; the free fraction of drug, as discussed earlier; and the ultrafiltration rate.
      ii. The ability of a substance to pass through a membrane by convection is termed the sieving coefficient (SC). The SC ranges from 0 to 1. A SC of 1 represents free movement, whereas a SC of 0 represents no movement across a filter.
      iii. SC is best obtained from the primary literature or from patient-specific values. It can be calculated using a ratio of measured drug or other solute in the ultrafiltrate to its concentration in the plasma, $SC = C_{UF}/C_p$, where C_{UF} is concentration in the ultrafiltrate and C_p is concentration in the plasma.
         (a) If a measured SC is not available, it can be estimated using the percent unbound to plasma protein, $SC = 1 - fb$, where fb is fraction bound (i.e., percent protein bound).
      iv. Site of replacement fluid administration can influence solute clearance. Adding replacement fluids pre-filter will dilute the blood entering the dialyzer. This diluted blood will have decreased drug concentrations; thus, less drug will be removed than if the replacement solution is infused after the filter.

         If pre-dilution (i.e., before the filter) fluids are used, clearance across the membrane is reduced. Clearance can be estimated using the following equation:

$$CVVH_{\text{pre-dilution}} = Q_{UF} \text{ x } SC \text{ x } Q_b/(Q_b + Q_{rf})$$

         where Q_{UF} is ultrafiltration flow rate, Q_b is blood flow rate, and Q_{rf} is pre-dilution replacement fluid flow rate. For pre-dilution fluid replacement to affect overall clearance, the rate must be high.

         If replacement fluids are administered postfilter (i.e., post-dilution), the clearance rate can be estimated using the following equation:

$$CVVH_{\text{post-dilution}} = Q_{UF} \text{ x } SC$$

   b. CVVHD
      i. Solute removal during CVVHD occurs by passive diffusion. The flow of dialysate is countercurrent to that of the blood. Movement of solute across the semipermeable membrane occurs because of a concentration gradient, with movement from an area of higher concentration (blood) to an area of lower concentration (dialysate). This process occurs until equilibrium is established.

- ii. Small substances (e.g., urea with an MW of 60 Da) are cleared more rapidly than larger substances (e.g., drugs with an MW greater than 500 Da).
- iii. The ability of a drug to cross the dialysis filter during CVVHD is called the saturation coefficient (SA). Equations exist for estimating the SA when published data are unavailable. It can be calculated as SA = C_E/C_p, where C_E is the concentration in the effluent (spent dialysate) fluid and C_p is the concentration in plasma. The CVVHD clearance can then be approximated by Q_d x SA, where Q_d is the dialysate flow rate.

c. CVVHDF
- i. Solute removal during CVVHDF is by diffusion and convection (i.e., both dialysate and replacement fluids are used).
- ii. Clearances of small substances are about equal to the sum of the clearance from CVVH and CVVHD separately. However, as MW increases, this correlation no longer holds true.
- iii. Clearance is estimated as CVVHDF = $(Q_{UF} + Q_d)$ x SA.

d. Prolonged intermittent KRT
- i. Limited literature is available to guide drug dosing during prolonged intermittent KRT modalities such as SLED and EDD.
- ii. Extended dialytic therapies of 8-12 hours may alter drug dosing intervals. For example, drugs with frequent dosing intervals (e.g., time-dependent antibiotics like β-lactams) may need to be administered more often during the run, given by extended infusion, or repeated/readministered after the prolonged intermittent KRT treatment.
- iii. Solute removal during SLED/EDD is greater than that during CVVHD when estimated over the same time interval because higher dialysis flow rates are used during SLED/EDD treatments.
- iv. General dosing considerations for SLED
  - (a) The duration of SLED and its flow rates (dialysate, blood) vary between studies and institutions, making a general approach to dosing problematic.
  - (b) In addition, little information is available to guide drug dosing.
  - (c) Like IHD and continuous KRT, the most important factors determining drug removal are protein binding, water solubility, MW (less than 500 kDa), and Vd (less than 0.8–1 L/kg); however, attention should also be given to the timing of drug administration relative to the prolonged intermittent KRT treatment.

e. Residual renal function may significantly contribute to drug clearance and requires consideration when determining dosing.
- i. In general, increased dosing for concentration-dependent antibiotics and extended infusion for time-dependent antibiotics should be used in patients with preserved diuresis (greater than 500 mL/d) compared with patients with anuria to achieve adequate pharmacokinetic/pharmacodynamic targets.

Patient Case

Questions 4–6 pertain to the previous case.
F.B. is a 68-year-old man (weight 70 kg) admitted to your ICU with fever, elevated WBC, respiratory failure requiring mechanical ventilation, and norepinephrine to support his blood pressure. His medical history is significant for chronic back pain, diabetes, and hypertension. He takes both enalapril and glipizide once daily, as well as acetaminophen as needed. Before this admission, he had otherwise been healthy, seeing his primary care provider about 1 week ago. At that time, his blood pressure was 140/80 mm Hg, and his A1C was 5.2%. His laboratory workup was also unremarkable: WBC 5.0 x 10^3 cells/mm^3, BUN 7 mg/dL, and SCr 0.9 mg/dL. Today, his WBC is 24 x 10^3 cells/mm^3, BUN 38 mg/dL, and SCr 3.2 mg/dL, with 325 mL of UOP since his admission 24 hours ago. It is determined that F.B. needs KRT to manage his volume and control his metabolic derangements. He is currently receiving norepinephrine with a mean arterial pressure of 65 mm Hg.

4. Which renal replacement mode will most likely be chosen?
   A. IHD.
   B. Slow-low EDD.
   C. Continuous KRT.
   D. Peritoneal dialysis.

5. F.B. will be initiated on a new extended-spectrum cephalosporin with limited information available for its use during continuous KRT. Given the following parameters, estimate the drug's SC: MW 480 Da, positively charged drug, Vd 1.9 L/kg, protein binding 12%.
   A. 0
   B. 0.52
   C. 1.9
   D. 0.88

6. Given the calculated SC, estimate the new cephalosporin's clearance during continuous KRT if the prescription is CVVH, blood flow 200 mL/minute, ultrafiltration rate 2000 mL/hour, 100% pre-filter replacement fluids, and use of a high-flux, high-efficiency dialyzer.
   A. 0.9 L/hour.
   B. 1.5 L/hour.
   C. 3.3 L/hour.
   D. 5.3 L/hour.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: C**

Both RIFLE class "F" and AKIN stage 3 are met using similar SCr and UOP criteria. For this case, the SCr increased by at least 3-fold above baseline, and the patient's UOP was less than 0.3 mL/kg/hour for 24 hours. Although A and B are true, the worse values in the RIFLE class and AKIN staging systems should be chosen when determining the class and stage of AKI. Answer D is incorrect because his renal indices have not been present for at least 3 months. Collectively, both the RIFLE and the AKIN criteria have been included in the KDIGO criteria, which is the current standard definition.

2. **Answer: A**

This patient has severe sepsis that led to decreased renal perfusion, causing AKI. Enalapril likely contributed to the injury by altering renal hemodynamics (Answer A is correct). Neither glipizide nor acetaminophen is likely to cause AKI (Answers B–D are incorrect).

3. **Answer: A**

Acute kidney injury cannot currently be diagnosed with a specific blood test or imaging study (Answer C is incorrect). The degree of kidney dysfunction and the patient's symptoms and coexisting diseases may provide clues regarding the etiology of the patient's kidney injury (Answer A is correct). Drug-induced AKI is most common in the setting of additional insults and may occur even after the drug is discontinued. Given a patient's history and presentation as well as a patient's physical examination, a clinician may pursue additional testing to find the DIKD phenotype. Serum markers (e.g., SCr, UOP) are often nonspecific (Answer C is incorrect); kidney biopsy is only warranted for certain DIKD phenotypes (e.g., AIN, glomerular diseases) and is often not pursued in the acute setting (Answer D is incorrect). Renal ultrasonography would be helpful for nephrolithiasis/crystalluria phenotypes or evidence of postrenal AKI not alleviated with urinary catheter placement (Answer B is incorrect).

4. **Answer: C**

Intermittent hemodialysis is often used in critically ill patients because many physicians are familiar with this therapy; however, about 20%–30% of patients receiving IHD become hypotensive and require discontinuation or a switch to an alternative therapy. Although prolonged intermittent KRT methods like SLED or EDD are an option, some form of continuous KRT would likely be chosen because of this patient's unfavorable hemodynamics. Continuous renal replacement therapies such as CVVH, CVVHD, and CVVHDF are often used because they allow for slower flow rates and improved hemodynamics. However, there is no clear benefit with one therapy over another.

5. **Answer: D**

Protein binding primarily determines drug clearance during KRT. Other factors that contribute to drug clearance include low MW and low Vd. Drug charge leading to dialyzer adhesion has only a limited effect on drug clearance during continuous KRT and has been poorly studied. When available, SC should be identified from the package insert information or the primary literature or calculated from the concentration of the solute in the ultrafiltrate divided by the concentration of the solute in the plasma. When unavailable, SC can be estimated as SC = 1 − fb. In this case, the SC = 1 – 0.12 = ~0.88 (Answer D is correct; Answers A–C are incorrect).

6. **Answer: B**

The general approach to calculating clearance during CVVH multiplies the SC (the degree to which a substance is able to pass through the membrane) by the ultrafiltration rate. If predilution (i.e., before the filter) fluids are used, clearance across the membrane is reduced, which must be accounted for in the formula. Clearance in that case can be estimated using the following equation: CVVHpre-dilution = Q^{UF} x SC x [Q^{b}/(Q^{b} + Q^{rf})] (where Q^{UF} is ultrafiltration flow rate (liters per hour), Q^{b} is blood flow rate [converted to liters per hour for consistent units], and Q^{rf} is predilution replacement fluid flow rate, as stated earlier). In this case, clearance = 2 L/hr x 0.88 x [12 L/hr/(12 L/hr + 2 L/hr)] = 1.5 L/hr (Answer B is correct; Answers A, C, and D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: A**

The drug-induced kidney disease phenotype most likely associated with these antibiotics is AIN from ceftriaxone. Acute interstitial nephritis is considered under the AKI phenotype (Answer A is correct). Azithromycin would unlikely cause drug-induced kidney disease. Although AIN is an overall uncommon cause of DIKD, in 75% of AIN cases, one or more drugs are involved. Several medications have been associated with this type of kidney disease, including penicillins, cephalosporins, sulfonamides, ciprofloxacin, vancomycin, NSAIDs and COX-2 inhibitors, proton pump inhibitors, immune checkpoint inhibitors, antiepileptic drugs, ranitidine, diuretics, and cocaine. This patient may have other contributing factors to AKI, including sepsis and shock. Glomerular disease, nephrolithiasis, and tubular dysfunction have not been associated with cephalosporins (Answers B-D are incorrect).

2. **Answer: C**

Stage 3 AKI is met by both the SCr criteria (3 x baseline) and the need for KRT (Answer C is correct; Answers A and B are incorrect). Urinary output is not needed to stage the kidney dysfunction in this case because the patient fulfills other criteria (Answer D is incorrect).

3. **Answer: C**

Answer C is correct. Drug-dosing recommendations for IHD can be found in many resources. However, dosing during continuous KRT and SLED/EDD is less clear. Primary literature and/or summary tables for continuous KRT and SLED should be referenced because these recommendations are not usually found in other sources (Answers A and B are incorrect). Use caution to ensure that identical modes of continuous KRT are referenced with similar flow rates. Drug dosing using a sieving coefficient should only be used when a review of the literature fails to provide specific drug adjustment recommendations (Answer D is incorrect).

4. **Answer: A**

Solute removal during CVVH is by convection, which is primarily influenced by membrane pore size, free fraction of drug, and ultrafiltration rate. Diffusion is the process of clearance during CVVHD making Answers B and C incorrect. Membrane binding does occur but is not the primary route of clearance during CVVH (Answer D is incorrect).

5. **Answer: A**

Answer A is correct. Protein binding is a primary determinant of drug clearance during continuous KRT. Only unbound drug can be cleared through the circuit; therefore, an increase in protein binding while other factors remain stable would lead to reduced drug elimination (Answers B and C are incorrect). A high Vd would reduce drug clearance (Answer D is incorrect). The impact of high Vd is more significant in IHD, resulting in less drug removal because there is little time during the 3- to 4-hour IHD run for a drug to redistribute out of the peripheral tissues.

Neurocritical Care

Keaton S. Smetana, Pharm.D., MBA, FNCS, FCCM
OhioHealth Riverside Methodist Hospital
Columbus, Ohio

Casey C. May, Pharm.D., FNCS, BCCCP
The Ohio State University College of Pharmacy
Columbus, Ohio

NEUROCRITICAL CARE

KEATON S. SMETANA, PHARM.D., MBA, FNCS, FCCM

OHIOHEALTH RIVERSIDE METHODIST HOSPITAL
COLUMBUS, OHIO

CASEY C. MAY, PHARM.D., FNCS, BCCCP

THE OHIO STATE UNIVERSITY COLLEGE OF PHARMACY
COLUMBUS, OHIO

Learning Objectives

1. Identify pertinent pathophysiologic and laboratory changes that acutely occur after neurologic injuries and require therapeutic intervention.
2. Describe monitoring devices commonly used in neurocritical care patients that help develop and optimize treatment strategies.
3. Develop an evidence-based treatment strategy for neurocritical care patients that optimizes patient outcomes and reduces the risk of adverse drug effects and drug interactions.
4. Recommend a monitoring plan to assess response to therapeutic regimens and specific therapeutic goals for neurocritical care patients.
5. Develop new plans of care for neurocritical care patients according to therapeutic and adverse outcomes and progress toward therapeutic goals.

Abbreviations in This Chapter

ADH	Antidiuretic hormone
CNS	Central nervous system
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CSWS	Cerebral salt-wasting syndrome
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
PSH	Paroxysmal sympathetic hyperactivity
RSE	Refractory status epilepticus
SAH	Subarachnoid hemorrhage
SCI	Spinal cord injury
SIADH	Syndrome of inappropriate antidiuretic hormone
SDOH	Social determinants of health
TBI	Traumatic brain injury
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 56-year-old woman is hospital day 4 after her acute aneurysmal subarachnoid hemorrhage (SAH). She is oriented and following commands. Laboratory values reveal a serum sodium of 128 mmol/L. Other serum chemistry values include potassium (K) 3.9 mEq/L, chloride 103 mEq/L, bicarbonate 27 mEq/L, blood urea nitrogen (BUN) 10 mg/dL, and serum creatinine (SCr) 1.0 mg/dL. Her urinary output is 1–2 mL/kg/hour, and her fluid balance has been +435 mL during the past 24 hours (currently receiving 0.9% sodium chloride at 125 mL/hour). Which is the best initial therapy for this patient's hyponatremia?

   A. Tolvaptan 20 mg orally daily.
   B. 1.5% sodium chloride infusion at 125 mL/hour.
   C. Water restriction to less than 1.5 L/day.
   D. No treatment indicated right now.

2. A 27-year-old woman is admitted with an acute ventriculoperitoneal shunt failure and associated infection. She has no significant medical history and no allergies to medications. A lumbar puncture reveals cerebrospinal fluid (CSF) white blood cell count (WBC) 34 × 10^3 cells/mm^3, red blood cell count (RBC) 1 × 10^3 cells/mm^3, protein 78 mg/dL, and glucose 21 mg/dL. The cultures grow methicillin-resistant *Staphylococcus epidermidis* (MRSE). Her shunt is externalized. Despite 4 days of intravenous vancomycin (most recent vancomycin trough was 17.7 mcg/mL), the CSF continues to grow MRSE. Which is the most appropriate intraventricular antimicrobial regimen to initiate for this patient's refractory ventriculitis?

   A. Give vancomycin 10 mg intraventricularly daily.
   B. Give gentamicin 5 mg intraventricularly daily.
   C. Give ampicillin 50 mg intraventricularly daily.
   D. No antimicrobials should be given intraventricularly for this patient.

3. A 25-year-old man is admitted after a two-story fall from a ladder. The initial computed tomography (CT) scan of his brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His post-resuscitation Glasgow Coma Scale (GCS) score is E1-M4-V1T. An intracranial pressure (ICP) monitor is placed with an opening pressure of 32 mm Hg and a cerebral perfusion pressure (CPP) of 53 mm Hg. Serum laboratory values include sodium (Na) 141 mEq/L, K 3.6 mEq/L, BUN 8 mg/dL, SCr 1.1 mg/dL, glucose 178 mg/dL, WBC 14.8 × 10^3 cells/mm^3, pH 7.46, and partial pressure of carbon dioxide (Pco_2) 34 mm Hg. Which supportive care issue is most relevant to the appropriate treatment of a patient with a severe traumatic brain injury (TBI)?

   A. Avoid enteral nutrition for the first 5–7 days because of the lack of gastrointestinal (GI) tolerance in severe TBI.
   B. Maintain CPP at 60–70 mm Hg to optimize perfusion and reduce complications.
   C. Provide dextrose 5% or other dextrose-containing intravenous fluids to compensate for the patient's increased metabolic needs.
   D. Initiate high-dose methylprednisolone therapy within 8 hours of injury to reduce cerebral edema.

4. A 69-year-old woman presents to the emergency department with a 30-minute history of difficulty with word finding and left upper-extremity weakness. Her NIH Stroke Scale score is 13. A head CT scan reveals no acute abnormalities. The patient's home medications include lisinopril, carvedilol, warfarin, and atorvastatin. Her medical history includes hypertension, atrial fibrillation, and transient ischemic attacks (diagnosed 6 months ago). Serum laboratory values include Na 145 mEq/L, K 4.0 mEq/L, BUN 18 mg/dL, SCr 1.2 mg/dL, glucose 132 mg/dL, WBC 8.7 × 10^3 cells/mm^3, hematocrit (Hct) 38.9%, platelet count (Plt) 355,000/mm^3, and international normalized ratio (INR) 1.5. Her vital signs include blood pressure 167/98 mm Hg, heart rate 132 beats/minute, oxygen saturation (Sao_2) 98%, and respiratory rate 14 breaths/minute. Which is the most appropriate next step in this patient's care?

   A. Initiate aspirin 324 mg orally × 1.
   B. Initiate alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
   C. Initiate nicardipine to reduce blood pressure to systolic blood pressure (SBP) less than 140 mm Hg, followed by alteplase 0.9 mg/kg intravenously (10% bolus dose, 90% infusion up to 90 mg maximum).
   D. Initiate vitamin K 10 mg intravenously × 1.

5. An 18-year-old man is admitted to the intensive care unit (ICU) after falling from a tree. Initial trauma screening reveals a C3–C4 fracture and dislocation with an incomplete spinal cord injury (SCI) at the corresponding levels (he has some sensory function bilaterally). The fracture has been reduced, and he arrives in the ICU 6 hours after injury. Which is the most appropriate statement related to initiating high-dose methylprednisolone therapy for this patient's SCI?

   A. May be used because he has an incomplete injury with some sensory function.
   B. Should be used because it will augment spinal perfusion.
   C. Should not be used because of the potential for adverse effects and questionable benefit.
   D. Should not be used because the patient is outside the treatment window.

6. A 27-year-old woman presents with fever, agitation, hypertension, and muscle rigidity. Her drugs-of-abuse screen is negative, and serotonin syndrome is a possible diagnosis. Which home medication is most likely a causative agent for serotonin syndrome?

   A. Buspirone.
   B. Levetiracetam.
   C. Cyproheptadine.
   D. Bupropion.

7. A 58-year-old woman with a Hunt and Hess grade 4 SAH resides in your ICU. She is day 6 after her SAH. Her current medications include 0.9% normal saline at 100 mL/hour, nimodipine 60 mg by feeding tube every 4 hours, norepinephrine 0.05 mcg/kg/minute (5 mcg/minute), famotidine 20 mg intravenously every 12 hours, docusate 250 mg by tube every 12 hours, and morphine as needed for headache. Current laboratory values include Na 144 mEq/L, K 4.1 mEq/L, SCr 0.6 mg/dL, serum osmolality 322 mOsm/L, and Hct 32.3%. Her blood pressure is 167/99 mm Hg, heart rate 133

beats/minute, respiratory rate 18 breaths/minute, Sa_{O_2} 99%, and central venous pressure 5 mm Hg. Her most recent transcranial Doppler velocities are mean middle cerebral artery 125/135 (right/left), with a corresponding Lindegaard ratio of 3.5/3.7 (right/left). Her ICP is currently 24 mm Hg. She has a Licox monitor placed in the hemisphere ipsilateral to her aneurysm, which currently reveals a partial pressure of brain tissue oxygen of 14%. She is intubated and on the ventilator. Her GCS score has decreased from 10 to 8 during the past hour. Which treatment would be most appropriate for this patient in the ICU?

A. Verapamil 2.5 mg intra-arterially × 1.
B. 3% sodium chloride 2.5 mL/kg intravenously × 1.
C. 20% mannitol 0.25 g/kg intravenously × 1.
D. 1 unit of packed RBCs.

8. Which sedative in an intubated patient is most desirable for a patient with a diagnosis of SAH currently having vasospasm?

A. Lorazepam 1 mg/hour.
B. Midazolam 4 mg/hour.
C. Morphine 2 mg/hour.
D. Propofol 25 mcg/kg/minute.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 3, 6
    b. Task B: 5
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1–4, 8
    b. Task B: 4, 14
    c. Task C: 2, 3
3. Domain 3: Professional Practice
    a. Task A: 1, 2, 4

I. HYPONATREMIA

A. Epidemiology: Hyponatremia (serum sodium less than 135 mEq/L) is common in patients with a neurologic injury (12%–43%). The most common form of hyponatremia in the neurocritically ill patient is hypotonic hyponatremia (Syndrome of Inappropriate Antidiuretic Hormone [SIADH] and Cerebral Salt-Wasting Syndrome [CSWS]), which are the only types of hyponatremia addressed in this chapter.

B. Diagnosis/Pathophysiology
   1. Laboratory tests (serum sodium) are needed to diagnose hyponatremia.
   2. Urine sodium, urine osmolality, serum osmolality, and measurement of intravascular volume may also help determine the specific pathogenesis for hyponatremia.

C. Causes
   1. Consideration of iatrogenic hyponatremia
   2. Typically caused by an increase in salt-free water or loss of serum sodium

D. Differentiating Between SIADH and CSWS
   1. Typically made by assessing intravascular volume. Patients with SIADH tend to be euvolemic or hypervolemic with hyponatremia because of excessive antidiuretic hormone (ADH) release, whereas patients with CSWS tend to be hypovolemic with hyponatremia because of inappropriate urinary excretion of sodium and extracellular fluid.
   2. Measure intravascular volume using a central venous pressure catheter or similar invasive monitoring.
   3. Noninvasive hemodynamic monitoring devices (e.g., blood pressure and heart rate)
   4. Monitor fluid balance, weights, skin turgor
   5. Echocardiogram to estimate ventricular filling pressures

E. Clinical Impact
   1. Hyponatremia may result in increased brain edema and elevated intracranial pressure (ICP).
   2. May cause neurologic symptoms such as delirium, agitation, tremor, seizure, or coma

Table 1. Differential Diagnosis for SIADH and CSWS[a]

	Serum Sodium (mEq/L)	Serum Osmolality (mOsm/L)	Urine Sodium (mEq/L)	Urine Osmolality (mOsm/L)	Intravascular Volume Status
SIADH	< 135	< 285	> 25	> 200	Euvolemia
CSWS	< 135	< 285	> 25	> 200	Hypovolemia

[a] Note: Medications, particularly diuretics, may alter serum or urine measurements of osmolality or sodium concentration.

CSWS = cerebral salt-wasting syndrome; SIADH = syndrome of inappropriate antidiuretic hormone.

Table 2. Hyponatremia Clinical Symptoms by Severity of Hyponatremia

Serum Sodium <120 mEq/L	Serum Sodium 120–130 mEq/L	Serum Sodium 130–135 mEq/L
• Headache • Restlessness • Lethargy • Seizures • Brain stem herniation • Respiratory arrest • Death	• Malaise • Unsteadiness • Headache • Nausea • Vomiting • Fatigue • Confusion • Anorexia • Muscle cramps	• Asymptomatic • Headache • Nausea • Vomiting • Fatigue • Confusion • Anorexia • Muscle cramps • Depressed reflexes

F. SIADH: Increased secretion of ADH (or vasopressin) results in increased water retention at the renal distal tubules.

Table 3. Typical Causes of SIADH

Neurologic & Pulmonary Disorders	**Medications**
TBI	Desmopressin/vasopressin
Brain tumor	Selective serotonin reuptake inhibitors
Stroke	Tricyclic antidepressants
Brain infection	Carbamazepine
Subarachnoid hemorrhage	Oxcarbazepine
Intracerebral hemorage	Chlorpropamide
Pneumonia/tuberculosis	Cyclophosphamide/iphosphamide
Lung cancer	Methylenedioxymethamphetamine
	Nicotine
	Opioids
	Phenothiazine antipsychotic medications
	Nonsteroidal anti-inflammatory drugs
	MDMA (ecstasy)

MDMA = 3,4-methylenedioxymethamphetamine; TBI = traumatic brain injury.

G. Treatment – Guidelines for diagnosing and managing hyponatremia are available (Intensive Care Med 2014;40:320-31).

Table 4. Treatment Strategies for SIADH

	Fluid Restriction	PO Sodium	IV Sodium	Demeclocycline	Vasopressin (V)-Antagonists
Mechanism of action	Restriction of free water results in increased impact of insensible losses, permitting sodium concentration to rise	Sodium supplementation	Sodium supplementation	Inhibition of ADH activity, possibly because of inhibition of aquaporin water channels	Inhibition of renal V2 vasopressin receptors (conivaptan V1A + V2 receptors; tolvaptan V2 only)

Table 4. Treatment Strategies for SIADH *(continued)*

	Fluid Restriction	PO Sodium	IV Sodium	Demeclocycline	Vasopressin (V)-Antagonists
Dose	< 1500 mL/day	4–16 g/day (1 g = 17 mEq of Na)	0.9%–3% at 0.5–1.5 mL/kg/hr	300 mg every 12 hr up to 1200 mg/day	Conivaptan: 20–40 mg IV daily Tolvaptan: 15–60 mg PO daily (Intensive Care Med 2014;40:320-31)
Efficacy	Modest, delayed (over 2+ days)	Modest, more effective for CSWS (over 2+ days)	Modest, more effective for CSWS (over 2+ days)	Modest, delayed (over 1 wk)	Modest, prompt over the first 24 hr
Common adverse effects	Thirst	Thirst, diarrhea, nausea, vomiting	Fluid overload, hyperchloremia	GI upset, hepatotoxicity, nephrotoxicity, photosensitivity	Thirst; conivaptan Infusion pain
Common considerations	Difficult to ensure adherence; caution for permitting hypovolemia in patients with cerebral perfusion needs such as SAH, TBI	Poor palatability when taken by mouth	≤ 3% sodium chloride may be given through peripheral IV line; The smallest-bore IV in the largest available vessel should be used. Central line remains the preferred access, if available	Chelation occurs with coadministered cations; nephrotoxicity has been reported	Cost; drug-drug interactions are common; risk of overcorrection of Na > 8 mEq/24 hours; tolvaptan should not be used > 30 days in patients with liver disease due to risk of life-threatening liver injury

ADH = antidiuretic hormone; IV = intravenous(ly); PO = oral(ly); SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

1. Treatment of SIADH can be challenging in neurocritical care patients such as those with subarachnoid hemorrhage (SAH) and TBI.
2. Treatment of choice is fluid restriction, which is typically not feasible in patients with SAH or TBI because of prioritizing a euvolemic volume status to optimize cerebral perfusion pressure (CPP). This is particularly important when treating elevated ICP or cerebral vasospasm.
3. Hypertonic sodium solutions are often needed to raise serum sodium.
4. A practice-based study evaluated the impact of various hyponatremia treatments on the serum sodium concentration (Neurocrit Care 2017;27:242-8). Hypertonic saline solutions were commonly used and most effectively increased the serum sodium.

H. Cerebral Salt-Wasting Syndrome (CSWS)
   1. Etiology is largely unknown, but speculation typically focuses on the increased secretion of natriuretic peptides, causing loss of sodium at the renal distal tubules.
   2. May also be associated with relative adrenal insufficiency
   3. Typical causes include TBI, SAH, and brain tumor.

4. Fludrocortisone 0.1–0.4 mg/day in divided doses may help reduce sodium loss in CSWS (Misra 2018; Lee 2008).
    a. An adverse effect of fludrocortisone is hypokalemia: Consider potassium supplementation.

I. Considerations for Rapid Correction of Hyponatremia
  1. Recommended increase in serum sodium concentration is 0.5 mEq/L/hour or less (Box 1).
  2. Patients with chronic hyponatremia, defined as hyponatremia that has been present for 48 hours or more or if the duration is unknown, may need to be corrected more slowly because of the equilibration of brain electrolytes with chronic hyponatremic state (N Engl J Med 2000;342:1581-9).
  3. Patients with acute hyponatremia, defined as hyponatremia that has developed over a period less than 48 hours, may tolerate quicker correction.
  4. Patients with severe neurologic symptoms because of hyponatremia appear to tolerate rapid correction of serum sodium. A strategy to rapidly correct sodium is to increase by 5 mEq/L in the first 1–2 hours, a maximum of 10 mEq/L in the first 5 hours, then 15–20 mEq/L in the first 48 hours (Crit Care Med 2017;45:1762-71).

Box 1. Common Equations Used for Sodium Correction in Hyponatremia

$$\text{Na requirement (mmol)} = \text{total body water } (0.6 \times \text{kg})^{a} \times (\text{desired Na} - \text{current Na})$$

$$\text{Infusion rate (mL/hr)} = (\text{Na requirement} \times 1000)/(\text{infusion Na concentration} \times \text{time})$$

[a] 0.6 for men, 0.5 for women; infusion Na concentration in millimoles per liter and time in hours.

Na = sodium.

Information from: Adrogue HJ, Madias N. Hyponatremia. N Engl J Med 2000;342:1581-9.

  5. Quicker correction in patients with severe symptoms (coma, seizures) may be prudent – Up to 1–2 mEq/L/hour for the first few hours
  6. Rapid correction necessitates frequent serum sodium monitoring (e.g., every 4 hours) to avoid overcorrection or too-rapid correction.
  7. Too-rapid correction of serum sodium may result in osmotic demyelination syndrome; a routine approach should be to limit Na increase to no more than 12 mEq/L in the first 24 hours or less than 18 mEq/L in the first 48 hours (Intensive Care Med 2014;40:320-31).

II. HYPERNATREMIA

A. Epidemiology
  1. Hypernatremia (serum sodium greater than 150 mEq/L) is also common in patients with neurologic injury.
  2. Incidence in SAH up to 22%
  3. Incidence in TBI up to 21%
  4. Hypernatremia and hyperchloremia are increasingly associated with an increased risk of acute kidney injury; thus, careful monitoring is warranted.

B. Diagnosis/Pathophysiology: Laboratory tests (serum sodium) are needed to diagnose hypernatremia. Urine sodium, urine osmolality (<250 mOsm/L), urine specific gravity (<1.004), urine volume, and serum osmolality (>300 mOsm/L) may also help determine the specific pathogenesis.

C. Typical Causes
  1. Consideration of iatrogenic hypernatremia
  2. Diabetes insipidus
    a. Decreased secretion of ADH or vasopressin results in decreased retention of water at the renal distal tubules. Observed in the setting of pituitary or hypothalmic damage (brain tumor, TBI) or brain death.
    b. Characterized by voluminous (greater than 250 mL/hour), dilute urinary output

D. Treatment
  1. Hypotonic solutions for free-water replacement
    a. Dextrose 5% in water
    b. 0.45% sodium chloride
    c. Water supplementation orally or by feeding tube
  2. Vasopressin analogs
    a. Supplementation of ADH to normal functional concentrations
    b. Titrate therapy to normalized urinary output, serum sodium correction, and urine specific gravity.
    c. Desmopressin
      i. Intravenously or subcutaneously: 0.5–4 mcg every 8–12 hours (usual starting dose 1–2 mcg)
      ii. Intranasally: 10–40 mcg/day divided into two or three doses (usual starting dose 10 mcg)
      iii. Orally: 50–800 mcg divided into two doses (usual starting dose 50 mcg)
      iv. May be dosed as needed, depending on initial laboratory values
    d. Patients after pituitary removal may more commonly require long-term therapy.
  3. Arginine vasopressin – Continuous infusion 1–15 units/hour (usual starting dose 1 unit/hour; titrate to urinary output of 150–250 mL/hour)
  4. Considerations for rapid correction of hypernatremia
    a. Recommended decrease in serum sodium concentration is 0.5 mEq/L/hour or less.
    b. Too-rapid correction of serum sodium may result in cerebral edema.
    c. In general, neurocritical care patients should receive minimal amounts of dextrose or free water–containing fluids to avoid the risk of cerebral edema.

III. STATUS EPILEPTICUS

A. Epidemiology – Incidence of status epilepticus is 18.3–41/100,000 people per year in the United States

B. Status Epilepticus – Continuous seizures for 5 minutes or more OR intermittent seizures without regaining consciousness in between seizures (Neurocrit Care 2012;17:3-23)
  1. Generalized convulsive status epilepticus: Generalized convulsions present with onset of seizure activity – Usually clinically evident
  2. Nonconvulsive status epilepticus: Typically occurs in comatose patients with no overt convulsions present (seizures noted with electroencephalogram [EEG] monitoring only)

C. Refractory Status Epilepticus (RSE) – Status epilepticus that persists after standard treatment (e.g., a benzodiazepine followed by another anticonvulsant medication)

D. Super-refractory status epilepticus – Failure to wean continuous anesthetic agent after 24–48 hours of burst suppression or termination of continuous EEG seizures

E. Diagnosis/Pathophysiology – Diagnostic tests
  1. Laboratory tests often show electrolyte abnormalities (particularly sodium, magnesium, and phosphorus), and serum lactate may be elevated in the acute period after seizure activity.
  2. EEG monitoring is necessary to identify and characterize seizures.
    a. Continuous monitoring is preferred in patients with status epilepticus to capture intermittent or fluctuating seizure patterns (Neurocrit Care 2012;17:3-23).
    b. Typical recommended duration is at least 48 hours, and monitoring should be initiated as soon as possible after suggestion or diagnosis of seizure.

F. Etiology (see Table 5).

Table 5. Typical Etiologies of Status Epilepticus

Cause of Status Epilepticus	Approximate % of Patients
Epilepsy	33–55
Miscellaneous	12–24
Stroke	14–22
Anticonvulsant nonadherence	20
Drug withdrawal	10–14
Brain tumor	10
Metabolic	10
TBI	7
Drug toxicity	5
CNS infection	3

CNS = central nervous system; TBI = traumatic brain injury.

G. Clinical Impact
  1. Mortality rate ranges from 9% (primarily in patients with preexisting epilepsy/anticonvulsant medication nonadherence) to 30% (in patients with a concomitant pathology such as TBI or stroke).
    a. Mortality in nonconvulsive status epilepticus is about double compared with overt seizures.
    b. Older adults have a higher mortality rate.
  2. Discharge disposition: 14%–18% of patients presenting to the emergency department in status epilepticus ultimately have a resultant neurologic deficit.

H. Agent Selection (Neurocrit Care 2012;17:3-23; Epilepsy Curr 2016;16:48-61): Note that the dosing regimens for first- and second-line therapies are for children and adults
  1. First-line therapy (emergent)
    a. Benzodiazepine therapy preferred; appropriate dosing is essential – Do NOT underdose first-line therapy
    b. Lorazepam 0.1 mg/kg intravenously (maximum 4 mg/dose) OR
    c. Midazolam 5–10 mg (or 0.2 mg/kg, maximum dose 10 mg) intramuscularly (preferred for patients with no intravenous access) OR
    d. Diazepam intravenously (0.15–0.2 mg/kg, maximum 10 mg/dose) or rectally (0.2–0.5 mg/kg, maximum 20 mg/dose) – Not recommended as first-line therapy for hospitalized patients because of short duration of seizure control

2. Second-line therapy (urgent): Initiate an anticonvulsant after benzodiazepine therapy if seizures persist or if a maintenance therapy needs to be initiated to prevent future seizures.
   a. In 2020, the ESETT trial (Lancet 2020;395:1217-24) demonstrated that any of the following three drugs, at the listed dose, can be used as a potential first choice for a second-line therapy in status epilepticus
      i. Valproate 40 mg/kg (maximum dose 3000 mg) intravenously
      ii. (Fos)phenytoin 20 mg/kg intravenously. (The ESETT Trial used a maximum dose of 1500 mg for blinding purposes but this is not recommended based on the PK/PD of [Fos]phenytoin.)
      iii. Levetiracetam 60 mg/kg (maximum dose 4500 mg) intraveously
3. Third-line therapy (refractory)
   a. If seizures persist after first- and second-line therapy, RSE should be treated aggressively and in a timely manner with continuous infusion anesthetic agents. The patient should be intubated before starting therapy.
   b. RSE agents should be titrated to burst suppression (the almost total elimination of electrical activity on EEG, except for short "bursts" of cortical activity [typically therapy is titrated to 2–5 bursts/minute]) or termination of electrographic seizure activity, depending on provider preference.
   c. Maintain established goal (burst suppression or termination of electrographic seizure activity) for 24–48 hours before trying to taper continuous agents. In addition, optimize maintenance anticonvulsant therapy before wean.
   d. Limited data exist supporting any one agent over another.
   e. Continuous infusion anesthetics for RSE titrated to target burst suppression
      i. Midazolam high-dose infusion 0.05–2 mg/kg/hour
      ii. Pentobarbital infusion (loading dose about 25 mg/kg total, continuous infusion 0.5–5 mg/kg/hour)
      iii. Propofol infusion 20–200 mcg/kg/minute
   f. Other options for RSE in intubated and/or nonintubated patients
      i. Can use any of the second-line agents listed above if they have not already been administered
      ii. Lacosamide 400 mg intravenously
      iii. Topiramate 200–400 mg orally/nasogastrically
      iv. Phenobarbital 20 mg/kg intravenously
      v. Perampanel 12 mg orally/nasogastrically
4. Super-refractory status epilepticus
   a. Treatment is typically reinitiation of continuous anesthetic agents used for RSE.
   b. Ketamine, an *N*-methyl-d-aspartate (NMDA) receptor antagonist, may also be considered. Ketamine may cause emergence psychosis and hallucinations, for which midazolam may help.
   c. Patients should have a workup for causes of super-refractory status epilepticus (e.g., autoimmune encephalitis including paraneoplastic syndromes and, infectious encephalitis).
5. Nonpharmacologic therapies if medical therapy fails
   a. Ketogenic diet: Limiting medications and nutrition to low-carbohydrate content; more likely to be successful in pediatric patients than in adult patients because of difficulty achieving ketosis in adults. Exact mechanism of action is unknown, but may increase sequestration of glutamate and decrease reactive oxygen species. Benefits typically occur within 1–3 months. Must modify diet targeting fat to carbohydrate plus protein in a 4:1 or 3:1 ratio
   b. Vagus nerve stimulation

I. Monitoring
   1. Continuous EEG monitoring is necessary for status epilepticus and RSE.
   2. Proactively monitor serum concentrations for agents such as (fos)phenytoin and valproic acid to ensure adequate concentrations and mitigate the risk of toxicity. Because of altered protein binding, obtaining a free level of highly bound medications is preferred.

Table 6. Characteristics of Agents for Status Epilepticus

Antiepileptic Drug	Dosing	Common Adverse Effects	Considerations
Lorazepam	0.1 mg/kg IV (slow IV push) (maximum 4 mg/dose); up to 8 mg total	Sedation, hypotension	IV formulation contains propylene glycol
Midazolam (intermittent)	0.2 mg/kg IM (maximum 10 mg/dose)	Sedation, hypotension	Short duration with IV bolus
Diazepam	0.15 mg/kg IV (slow IV push); typically up to 10 mg total 0.2 mg/kg rectally (20 mg maximum)	Sedation, hypotension	IV formulation contains propylene glycol; rectal administration may be considered
Fosphenytoin	20 mg PE/kg IV (not to exceed 150 mg PE/min); may also give IM	Hypotension, arrhythmia, hepatotoxicity	Several drug-drug interactions
Phenytoin	20 mg/kg IV (not to exceed 50 mg/min)	Hypotension, arrhythmia, phlebitis, purple glove syndrome, hepatotoxicity	Several drug-drug interactions, IV formulation contains propylene glycol and ethanol. Addition of parenteral phenytoin to dextrose and dextrose-containing solutions should be avoided because of lack of solubility and resultant precipitation
Valproic acid	40 mg/kg IV (not to exceed 6 mg/kg/min)	Hyperammonemia, thrombocytopenia, hepatotoxicity	Many drug-drug interactions, avoid in patients with a TBI
Levetiracetam	60 mg/kg IV (maximum 4.5 g)	Sedation/paradoxical excitation, irritability	Renally eliminated, limited drug-drug interactions
Lacosamide	400 mg IV (typically over 15–30 min)	Dizziness, bradyarrhythmia, P-R interval prolongation	Limited drug-drug interactions
Topiramate	PO/enteral loading dose of 300–800 mg, followed by a daily dose of 400–1000 mg in 2–3 doses	Metabolic acidosis, nephrolithiasis	No IV formulation available
Phenobarbital	20 mg/kg (not to exceed 100 mg/min)	Sedation, hypotension, respiratory depression	IV formulation contains propylene glycol

Table 6. Characteristics of Agents for Status Epilepticus *(continued)*

Antiepileptic Drug	Dosing	Common Adverse Effects	Considerations
Pentobarbital	10 mg/kg (typically over 15–30 min, depending on blood pressure); typically need additional 5 to 10 mg/kg boluses to full loading dose of 25–30 mg/kg; 1 to 3 mg/kg/hr infusion	Sedation, hypotension, respiratory depression, constipation, cardiac depression, immunosuppression	IV formulation contains propylene glycol; target is burst suppression; several drug-drug interactions
Midazolam high-dose infusion	0.05–2 mg/kg/hr	Sedation, hypotension, respiratory depression	Potential tachyphylaxis, target is burst suppression
Propofol	20–200 mcg/kg/min, titrate by 5 mcg/kg/min; use caution when administering doses > 80 mcg/kg/min for extended periods	Sedation, hypotension, respiratory depression, pancreatitis, propofol-related infusion syndrome	Target is burst suppression; provides 1.1 kcal/mL; hypertriglyceridemia at higher doses
Ketamine	0.5–10 mg/kg/hr	Excitation, hypertension, possible neurotoxicity, hallucinations	May be more effective in prolonged refractory status epilepticus. May cause hypotension in patients with decreased shock index; consider IV fluid volume with high-dose infusions

AES = American Epilepsy Society; BID = twice daily; IM = intramuscular(ly); NCS = Neurocritical Care Society; PE = phenytoin equivalents; QID = four times daily.

Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23; Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48-61.

Patient Case

1. A 37-year-old man (weight 75 kg) is admitted to the emergency department with meningitis. On admission, his GCS score decreases from E3-M6-V1T to E1-M5-V1T over 10 minutes, and his nurse notices facial twitching. An EEG is ordered. Current medications include famotidine 20 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, docusate 100 mg nasogastrically twice daily, and a supplemental vitamin infusion for potential alcohol withdrawal. Which is the best acute therapy for this patient's suspected seizure activity?

   A. Fosphenytoin 1500 mg PE intravenously × 1.
   B. Valproic acid 1500 mg intravenously × 1.
   C. Midazolam 10 mg intramuscularly × 1.
   D. Levetiracetam 1 g intravenously × 1.

IV. CENTRAL NERVOUS SYSTEM INFECTION: INTRAVENTRICULAR ANTIBIOTIC ADMINISTRATION

A. Case Selection
   1. Recommended in adult patients with cerebral spinal fluid (CSF) shunt or ventriculostomy infections for difficult-to-eradicate pathogens or for patients who cannot undergo the surgical component of therapy
   2. May also be considered in patients receiving systemic therapy who have responded poorly to systemic antimicrobial therapy alone (Clin Inf Dis 2017;64:e34-65)
   3. Not recommended for neonatal or infant central nervous system (CNS) infection

B. Desired Properties of Intraventricular Medications
   1. Preservative-free formulations
   2. Formulations' osmolality is close to that of the CSF (281 mOsm/L) when possible. Do not use diluents containing dextrose, whenever possible because of potential osmolality concerns
   3. Do not use medications known to lower the seizure threshold (e.g., β-lactams).
   4. pH similar to the CSF when possible (7.27–7.37).
   5. Total volume ideally less than or equal to 3 mL

C. Appropriate Dosing
   1. Intravenous plus intraventricular is recommended.
   2. Daily dosing is usually necessary; may need to adjust according to the amount of CSF drainage from external ventricular drain
   3. After drug instillation, the ventriculostomy tubing should be clamped for at least 15 minutes to allow the medication to equilibrate in the CSF before reopening the drain. Patients with high intracranial pressure may not tolerate this, so the ventriculostomy should be clamped for as long as the patient can tolerate, with close monitoring of the ICP.

Table 7. Various Antimicrobials and Doses for Intraventricular Administration

Antimicrobial	Daily Dose/Volume (adults)	Approximate Osmolality (mOsm/kg)	Common Adverse Effects
Vancomycin	10–20 mg/1 mL of NS	291	Headache, mental status changes, possible hyponatremia
Gentamicin	4–8 mg/1 mL of NS	293	Seizures
Tobramycin	4–8 mg/1 mL of NS	283	Seizures
Amikacin	30 mg/1 mL of NS	383	Seizures
Polymyxin B	5 mg/1 mL of NS	10	Hypotonia, seizures, meningeal inflammation
Colistimethate	10 mg/3 mL of NS	367	Meningeal inflammation
Amphotericin B deoxycholate	0.5 mg/3 mL of SWI	256 (in dextrose 5%)	Nausea, vomiting
Daptomycin	5 mg/2 mL of NS	364	Unknown

NS = normal saline; SWI = sterile water for injection.

Cook AM, Mieure KD, Owen RD, et al. Intracerebroventricular administration of medications. Pharmacotherapy 2009;29:832-45; Mueller SW, Kiser TH, Anderson TA, et al. Intraventricular daptomycin and intravenous linezolid for the treatment of external ventricular-drain-associated ventriculitis due to vancomycin-resistant *Enterococcus faecium*. Ann Pharmacother 2012;46:e35.

V. INTRACRANIAL PRESSURE TREATMENT

A. General Concepts
  1. Elevated ICP decreases tissue perfusion and tissue oxygenation and worsens neurologic outcome.
  2. Monro-Kellie doctrine: ICP equals cerebral blood volume (10%) plus CSF (10%) plus brain tissue (80%). Each therapy targeted at decreasing ICP acts on one or more of these components.
  3. Most practitioners use a stepwise approach to treating elevated ICP, including the following interventions:
    a. Head-of-bed elevation (30–45 degrees): Optimizes venous return from the brain, reducing venous pooling
    b. Early treatment of fever (greater than or equal to 37.8°C) to maintain normothermia.
    c. Osmotherapy (mannitol or hypertonic saline)
    d. Acute hyperventilation: Reduction in $P\text{CO}_2$ to around 32 mm Hg causes a compensatory vasoconstriction, which reduces cerebral blood volume (chronic hyperventilation should be avoided because of complications such as stroke).
    e. Drainage of CSF by a ventriculostomy
    f. Sedation with or without neuromuscular blockade (avoid benzodiazepines, when possible)
    g. Maintenance of CPP at 60–70 mm Hg
    h. Surgical decompression or hemicraniectomy (depending on the clinical scenario)
    i. Pharmacologic coma (pentobarbital)
    j. Hypothermia (33°C–36°C) – Clinicians should consider the risk-benefit of moderate hypothermia versus targeted temperature management for control of ICP.

B. Treatment Thresholds
  1. Recommendations are to treat sustained (for greater than 5 minutes) ICP greater than 22 mm Hg as measured by external ventricular drain, intraparenchymal catheter, or bolt (Neurosurgery 2017;80:6-15). If subarachnoid hemorrhage, symptom-based dosing over ICP targets is suggested (Neurocrit Care 2020;32;647-66).
  2. Specific ICP threshold may have interpatient variability.
  3. CPP ideally within 60–70 mm Hg
    a. Targeting CPP greater than 80 mm Hg routinely is also associated with an increased incidence of acute respiratory distress syndrome and mortality in patients with a TBI; thus, patients must be selected carefully when targeting higher ranges of CPP (Crit Care Med 1999;27:2086-95).
    b. Osmotherapy

C. Comparison of Osmotherapy Agents

Table 8. Comparison of Osmotherapy Agents

	Mannitol	**Hypertonic Saline**
Mechanism of action	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain Osmotic diuretic	Acute increase in cerebral blood flow results in cerebral vasoconstriction (because of autoregulation), leading to decreased cerebral blood volume Increase in serum osmolality creates osmotic gradient to pull extracellular fluid from brain

Table 8. Comparison of Osmotherapy Agents (*continued*)

	Mannitol	**Hypertonic Saline**
Typical dose	0.5–1 g/kg over 15 min (0.2-micron filter) Up to 1.6 g/kg if acute herniation	3%: 2.5–5 mL/kg over 15 min 7.5%: 1–2 mL/kg over 15 min 23.4%: 30 mL over 15 min (may infuse over 5–10 minutes in acute herniation)
Monitoring values	Serum: Osmolality, BMP (Na, K, SCr, BUN, glucose), osmolar gap Urine: Urinary output	Serum: Osmolality, Na, SCr, K Urine: Urinary output
Adverse effects	Hyper/hyponatremia Hypokalemia Renal failure Hypovolemia Rebound cerebral edema (?)	Hypernatremia Hypokalemia Hyperchloremic acidosis Renal failure Osmotic demyelination syndrome (?)

O'Brien SK, Koehl JL, Demers LB, Hayes BD, Barra ME. Safety and tolerability of 23.4% hypertonic saline administered over 2 to 5 minutes for the treatment of cerebral herniation and intracranial pressure elevation. *Neurocrit Care*. 2023;38(2):312-319. https://doi.org/10.1007/s12028-022-01604-1

1. Metabolic acidosis may occur after several hypertonic saline doses as the result of hyperchloremia.
    a. In patients with acidemia, which complicates ventilator management or other aspects of care, a combination of sodium chloride and sodium acetate may be considered to maintain the hyperosmolarity of the solution but reduce chloride provision (Crit Care Med 1999;26:440-6).
    b. Sodium bicarbonate 8.4% may also be considered for acute ICP elevations when other osmotherapy options are not immediately available, such as in patient care areas that do not typically care for neurologic ICU patients or patients with a TBI (Neurocrit Care 2010;13:24-8).
2. Monitoring osmolar changes with mannitol: The traditional serum osmolality threshold was 320 mOsm/L when using mannitol.
    a. Theory was that serum osmolality values greater than 320 were associated with renal dysfunction.
    b. Osmolar gap appears to be a more appropriate and accurate method of evaluating renal dysfunction risk with mannitol.
    c. Approximates the mannitol concentration
    d. Osmolar gaps greater than 55 mOsm/kg have been associated with renal dysfunction; however, many centers choose to target a goal osmolar gap less than 20–30 mOsm/kg prior to re-dosing mannitol.
    e. Calculation of osmolar gap (Box 2)

Box 2. Calculation of Osmolar Gap

$$\text{Osmolar gap} = \text{measured osmolality} - \text{estimated osmolality}$$
$$\text{Osmolar gap} = \text{measured osmolality} - [(2 \times \text{Na}) + (\text{BUN}/2.8) + (\text{glucose}/18)]$$

D. Sedation – Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing, reduced agitation, decreased cerebral metabolic rate ($CMRO_2$)
  1. Propofol is typically the preferred sedative – Quick onset, short acting, less accumulation with prolonged duration
      a. Patients with a TBI (and other neurologic injuries) require frequent, accurate neurologic examinations to evaluate the evolution of the neurologic injury.
      b. Hypotension risk may be harmful in specific patient types (e.g., aneurysmal SAH/vasospasm, TBI, SCI).

      c. In contrast to midazolam, propofol is advantageous because of its short half-life and relative lack of residual sedative effects.
   2. Benzodiazepines
      a. Not preferred because of long duration of action
      b. Also associated with delirium and cognitive impairment
      c. Potential for withdrawal effect, seizures
   3. Dexmedetomidine
      a. No specific considerations in existing guidelines for neurocritical care patients
      b. Hypotension risk may be harmful in specific patient types (e.g., aneurysmal SAH/vasospasm, TBI, SCI).
      c. May be particularly helpful in patients with paroxysmal sympathetic hyperactivity (PSH) ("storming") and facilitating extubation, managing alcohol withdrawal, and sedation requiring frequent neurologic assessments (DEXPRONE study; J Crit Care 2020;60:79-83)

E. Neuromuscular Blockade
   1. Mechanism of action: Decreased systemic oxygen delivery needs; reduced coughing
      a. Neuromuscular blockers have no intrinsic value for reducing ICP, but they may be helpful in select patients with specific issues that exacerbate ICP elevations.
         i. Prevention of cough, ventilator dyssynchrony (both increase ICP)
         ii. Control P_{CO_2} (increased P_{CO_2} may also increase ICP)
      b. Prevention of shivering during therapeutic hypothermia or targeted temperature management
      c. Reduces intrathoracic pressure
      d. May be essential in patients requiring high positive end-expiratory pressure (increased intrathoracic pressure may increase ICP)
   2. Various agents may be useful – Depends on patient organ function, prescriber preference
      a. Vecuronium/Rocuronium (particularly if normal organ function)
      b. Cisatracurium (particularly if end-organ dysfunction)
      c. Avoid atracurium, if possible, because of hypotension risk. Laudanosine, a hepatically metabolized product of Hofmann elimination, is a CNS stimulant that can accumulate with prolonged use.
   3. Monitor by train-of-four (goal 1-2/4 twitches with no clinical evidence of neuromuscular function [e.g., overbreathing the ventilator rate]).

F. Metabolic Suppression (pentobarbital)
   1. Mechanism of action: Suppression of electrical activity in brain (i.e., "burst suppression") causes reduced cerebral metabolic rate of oxygen ($CMRO_2$).
   2. Reduced $CMRO_2$ leads to decreased cerebral blood volume.
   3. Pentobarbital sodium is usually used in the United States (thiopental in Europe). When pentobarbital is initiated, all other sedatives and paralytics should be weaned off after burst suppression is achieved.
   4. Risks may outweigh benefit, at least for certain conditions such as large hemispheric infarction.
   5. Pentobarbital is no more effective and is potentially more harmful for first-line therapy for ICP control than mannitol – Early studies led clinicians to begin using pentobarbital only in patients with refractory ICP elevations (Can J Neurosurg 1984;11:434-40).
   6. Typical pentobarbital dosage
      a. 25–30 mg/kg intravenous loading dose. Usually given as 10 mg/kg × 1 dose, followed by 5 mg/kg every hour × 3 or 4 doses to avoid hypotension with large bolus dose
      b. 1- to 5-mg/kg/hour infusion after loading dose
   7. Titration
      a. Titrated to goal ICP (usually less than 20 mm Hg)

   b. Burst suppression on continuous EEG (target usually is 2–5 bursts/minute) is a surrogate end point for need of additional pentobarbital doses.
   c. A bolus dose is required concomitantly with an infusion titration because of its long half-life (24–48 hours) and rapid redistribution.
8. Monitoring
   a. ICP
   b. EEG and burst occurrence per minute
   c. Serum concentrations do not correlate well with ICP response and should not be used to titrate infusion. May be useful when therapy has been discontinued as part of brain death examination (to rule out continued intoxication from pentobarbital)
   d. Due to the risk of metabolic acidosis from propylene glycol accumulation, serum chemistry, pH, and osmolality should be monitored during prolonged treatment.
9. Adverse effects
   a. Hypotension as the result of several different causes
      i. Propylene glycol diluent
      ii. Direct vasodilator
      iii. Reduction in sympathetic tone because of metabolic suppression
      iv. Cardiac depressant (particularly with high doses and duration greater than 96 hours)
   b. Bradycardia
   c. Decreased GI motility and ileus
      i. Difficulty with enteral nutrition
      ii. Caloric needs are usually around 80%–90% of basal energy needs, so a lower flow rate for enteral nutrition is permissible.
      iii. Ideally, would use an elemental or semi-elemental nutrition product because stooling is rare on pentobarbital infusion
   d. Infection (particularly pneumonia)
   e. Immunosuppression
   f. Withdrawal seizures may occur.
   g. Metabolic acidosis due to propylene glycol toxicity

Patient Case

2. A 25-year-old man (weight 80 kg) is admitted after a two-story fall from a ladder. The initial CT scan of his brain reveals a large right temporal subdural hematoma, an overlying skull fracture, and a left temporal contusion. His post-resuscitation GCS is E1-M4-V1T. An ICP monitor is placed with an opening pressure of 32 mm Hg, and CPP is 53 mm Hg. Serum laboratory values include Na 139 mEq/L, K 3.6 mEq/L, BUN 42 mg/dL, SCr 2.4 mg/dL, glucose 178 mg/dL, WBC 14.8 × 10^3 cells/mm^3, pH 7.46, and P_{CO_2} 34 mm Hg. Which is the best initial therapy for this patient's elevated ICP?
   A. Mannitol 20% 1 g/kg intravenously × 1.
   B. 23.4% sodium chloride 30 mL intravenously × 1.
   C. Pentobarbital 10 mg/kg intravenously × 1.
   D. Midazolam 10 mg intravenously × 1.

G. TBI Guidelines (Neurosurgery 2017;80:6-15). The fourth edition of these guidelines was published in 2017; these are "living guidelines" that will be updated continuously. Unfortunately, the newest guidelines reflect only recommendations with high levels of evidence. Therefore, the 2007 guidelines may be needed to review practical recommendations (based on all levels of evidence) for complications in patients with a TBI.

1. Seizure prophylaxis
    a. Recommended as an option for prevention of early posttraumatic seizures (first 7 days after event)
    b. Phenytoin/fosphenytoin is the most commonly recommended agent (because of support for use from prospective clinical trials) (N Engl J Med 1990;323:497-502).
    c. Levetiracetam is also commonly used, despite a paucity of data (monitor for pronounced behavioral adverse effects in patients with neurologic injury).
    d. Valproic acid is as effective as phenytoin, but a trend toward increased mortality was observed in a prospective clinical trial; thus, it is usually avoided if possible (J Neurosurg 1999;91:593-600).
    e. Use of anticonvulsants for prevention of late seizures (after 7 days) has not been proven effective (not recommended).
2. CPP modulation
    a. CPP = mean arterial pressure (MAP) minus ICP.
    b. Surrogate for global cerebral perfusion
    c. Recommended goal is 60–70 mm Hg.
    d. Ideal CPP may have interpatient variability because of the patient's medical history and unique characteristics of the TBI.
    e. Patients with refractory elevations in ICP or who have a history of poorly treated hypertension (right shift of autoregulatory curve) may require a higher CPP.
3. Fluid resuscitation with or without vasopressor therapy
    a. Norepinephrine or phenylephrine are the preferred vasopressors for this indication.
4. Supportive care – Venous thromboembolism (VTE) prophylaxis
    a. Patients with a TBI have an increased risk of VTE because of:
        i. TBI-related coagulopathy
        ii. Delay in initiation of pharmacologic VTE prophylaxis
        iii. Immobility
        iv. Concomitant injuries (in polytrauma)
    b. Mechanical prophylaxis should be initiated as soon as possible.
    c. Pharmacologic prophylaxis should be initiated after intracranial bleeding is stabilized.
        i. Typically, 24–48 hours after event
        ii. May depend on coagulopathy on admission, extension of bleeding on CT scan, and other factors
        iii. Unfractionated heparin (every 8 hours) or low-molecular-weight heparin may be used for pharmacologic prophylaxis. In patients with normal renal function, low-molecular-weight heparin is preferred in those with polytrauma, particularly long bone or pelvic fractures.

H. Nutrition Support
1. Initiating nutrition support within 48 hours improves immune competence and may improve neurologic outcome (Crit Care Med 1999;27:2525-31).
2. Gastric feeding is not well tolerated in patients with a TBI, particularly during the first 5–7 days and particularly in those with an elevated ICP (causes decreased gastric motility). Postpyloric feeding access should be established as soon as possible.
3. Metabolic needs are elevated after a TBI (typically proportional to the severity of injury).
    a. Patients with a TBI typically require 120%–160% of basal metabolic needs.
    b. Metabolic cart/direct calorimetry can be used to better evaluate caloric needs.

I. Prevention of Stress-Related Mucosal Bleeding
1. Patients with a TBI have an increased risk of stress-related mucosal bleeding.
    a. Hypotension associated with a TBI or trauma
    b. Hypersecretion of acid associated with neurologic injury (Cushing ulcers)

    c. Potential for coagulopathy
    d. Need for mechanical ventilation
2. Almost all patients with a severe TBI should receive prophylaxis for stress-related mucosal bleeding (MacLaren 2024).
    a. Histamine-2 receptor antagonists (H_2RAs) have traditionally been the preferred agents.
    b. Proton pump inhibitors (PPIs) also raise gastric pH, permit hemostasis in areas of gastritis, and are associated with reduced clinically relevant important upper GI bleeding.
    c. Recent meta-analyses have suggested that PPIs are superior to H_2RAs, but a well-powered clinical trial has not been completed in the ICU or the neurologic ICU population.
    d. Which agent to select may depend on:
        i. Medications taken at home before admission
        ii. Presence of GI bleeding on admission

J. Glycemic Control
1. Hyperglycemia is associated with increased mortality in TBI.
2. Potential mechanisms
    a. Glucose toxicity in neurons
    b. Surrogate for severity of injury
    c. Exacerbation of cerebral edema
3. Avoid administering dextrose 5% and other hypotonic glucose-containing fluids.
4. Glycemic goals
    a. Prevent hyperglycemia (greater than 180 mg/dL)
    b. 140–180 mg/dL seems reasonable to avoid hypoglycemia.
    c. Caution should be used with glucose values in the low-normal range because of the risk of hypoglycemia.
    d. Hypoglycemia is associated with a worse outcome in TBI.
        i. Glucose obligate substrate for neurons
        ii. Threshold for glucose needs may be altered in TBI.
        iii. May increase seizure risk

K. Steroids
1. High-dose methylprednisolone plays no role in the treatment of inflammation or edema associated with TBI.
2. Large, prospective, randomized clinical trial showed increased mortality in steroid group compared with placebo (CRASH) (Lancet 2005;365:1957-9).

L. Pharmacokinetic Alterations
1. Altered volume of distribution: Patients with a TBI have increased volume of distribution because of the following:
    a. Fluid resuscitation
    b. Reduced plasma protein binding (particularly with albumin as a negative acute-phase reactant)
    c. Transient increased permeability of blood-brain barrier
2. Hepatic metabolism induction
    a. TBI increases hepatic metabolic capacity (extent to which is likely proportional to severity of injury).
    b. Results in more effective clearance of hepatically metabolized medications
    c. Increased dosing requirement for commonly used agents such as phenytoin, midazolam
    d. Induction subsides over time (usually 1–3 months, but varies by patient).

   e. Hypothermia during TBI may also reduce the induction of hepatic metabolism/cause metabolic rate of medications to be less than baseline.
3. Augmented renal clearance
   a. Increase in glomerular filtration rate (e.g., CrCL greater than 120 mL/min)
   b. Fluid resuscitation
   c. Increased endogenous catecholamines and glucocorticoid response
   d. Results in more effective clearance of renally eliminated medications
   e. Increased dosing requirement for commonly used agents such as vancomycin, aminoglycosides, β-lactams (J Trauma Acute Care Surg 2016;81:1115-21; Neurocrit Care 2015;23:374-9; Clin Pharmacokinet 2010;49:1-16; Pharmacotherapy 2019;39:346-54)
   f. Augmented renal clearance tends to subside over time (usually after first 7–10 days, but varies by patient).

VI. PAROXYSMAL SYMPATHETIC HYPERACTIVITY (I.E., "BRAIN STORMING")

A. Epidemiology
   1. About 8%–33% incidence in survivors of acquired brain injury
   2. Commonly associated with TBI (specifically diffuse axonal injury and high-burden parenchymal lesions), but may occur with other CNS insults

B. Diagnosis
   1. Typically, a diagnosis of exclusion and includes three or more symptoms in a cyclic fashion or episodically when the patient is stimulated (Baguley 2014).
      a. Fever
      b. Tachycardia
      c. Hypertension
      d. Tachypnea
      e. Dyspnea
      f. Diaphoresis
      g. Muscle rigidity (posturing)
   2. Common triggers
      a. Pain
      b. Bladder distension
      c. Turning
      d. Tracheal suctioning
      e. Typically unprovoked (hence "paroxysmal")

C. Pathophysiology largely unknown, but thought to be caused by somatosympathetic activation and heightened activity of brain stem after brain injury

D. Paroxysmal Sympathetic Hyperactivity (PSH) Assessment Measure: A tool to determine the possibility of PSH at that specific time has two components – Diagnosis Likelihood Tool and Clinical Feature Scale (J Neurotrauma 2014;31:1515-20)

Table 9. Preventive and Abortive Therapies for Paroxysmal Sympathetic Hyperactivity

Preventive Therapies	Abortive Therapies
Baclofen IT (titrated according to patient response) Bromocriptine 1.25 mg enterally BID (up to 40 mg/day) Clonidine 0.1–0.3 mg enterally three times daily Gabapentin 100–300 mg three times daily (up to 4800 mg/day) Propranolol 20–60 mg enterally every 4–6 hr	Baclofen IT (titrated according to patient response) Dantrolene 0.25–2 mg/kg IV every 6–12 hr Dexmedetomidine 0.2–1.5 mcg/kg/hr IV[a] Diazepam 5–10 mg IV PRN Fentanyl 25–100 mcg IV PRN Morphine 2–8 mg IV PRN[a] Propranolol 1–3 mg IV every 4 hr[a]

[a] Most common treatments.

IT = intrathecal; PRN = as needed.

Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. Curr Treat Options Neurol 2008;10:151-7; Thomas A, Greenwald BD. Paroxysmal sympathetic hyperactivity and clinical considerations for patients with acquired brain injuries: a narrative review. Am J Phys Med Rehabil 2019;98:65-72.

VII. ACUTE ISCHEMIC STROKE

A. Epidemiology
   1. Fifth leading cause of death and number 1 cause of disability in the United States, with around 800,000 strokes in the United States annually
   2. 85% of strokes in the United States are ischemic.

B. Diagnosis/Pathogenesis
   1. Diagnostic tests
      a. Neurologic examination
      b. Vital signs
      c. NIH Stroke Scale (greater than 25 is severe, range 1–42)
      d. Imaging and other tests (Stroke 2019;50:e344-418)
         i. Noncontrast CT scan or magnetic resonance imaging (MRI) of the brain (to rule out bleeding)
         ii. CT angiography (for patients with evidence of large vessel occlusion)
         iii. CT or MRI perfusion and diffusion imaging may be considered for patients outside the thrombolysis window.
         iv. Chest radiography (if lung disease is suspected)
         v. Lumbar puncture (if SAH is suspected and CT scan is negative for blood)
         vi. EEG (if seizures are suspected)
   2. Laboratory tests
      a. Blood glucose
      b. INR, activated partial prothrombin time (consider thrombin time, anti–factor Xa [anti-Xa] activity for direct oral anticoagulants)
      c. Complete blood cell count (CBC)
      d. Tests for hypercoagulable state

C. Causes
   1. Cardioembolic (29.1%)
   2. Large-artery atherosclerosis (16.3%)
   3. Lacunar infarcts (15.9%)

4. Unknown (36.1%)
5. Other (2.6%)

D. Treatment Considerations (2019;50:e344-418)
   1. 1. Thrombolysis
      a. Alteplase 0.9 mg/kg (maximum 90 mg) within 4.5 hours of symptom onset; 10% of total dose as intravenous bolus, followed by 90% as 60-minute intravenous infusion.
      b. Tenecteplase 0.25 mg/kg intravenous bolus (maximum 25 mg) within 4.5 hours of symptom onset may also be considered for off-label use in patients with acute ischemic stroke because it was found to be noninferior to alteplase (Lancet 2022;400:161-9), and was found to be superior in patients who are also eligible for mechanical thrombectomy (NEJM 2018;378:1573-82).
      c. In patients with acute ischemic stroke who awake with stroke symptoms or have unclear time of onset more than 4.5 hours from last known well, or at baseline state can undergo MRI to help select those who can benefit from intravenous alteplase administration within 4.5 hours of stroke symptom recognition (NEJM 2018;379:611-22).
      d. Goal SBP after receiving thrombolytics is less than 180 mm Hg and goal diastolic blood pressure (DBP) is less than 105 mm Hg.

Table 10. Typical Inclusion/Exclusion Criteria for IV Alteplase and Tenecteplase for Ischemic Stroke[a]

Patient Selection Criteria	Patient History Excludes All Contraindications
Onset of symptoms < 4.5 hr from drug administration Baseline head CT excludes intracerebral hemorrhage (ICH) or other risk factors Age ≥ 18 yr Vital signs and laboratory values: INR ≤ 1.7 Plt ≥ 100,000/mm^3 Blood glucose > 50 mg/dL Blood pressure control (SBP < 185 mm Hg, DBP < 110 mm Hg)	Intracranial or intraspinal surgery within 3 mo Head trauma or stroke < 3 mo Active internal or intracerebral bleeding Symptoms suggestive of SAH Any history of ICH Intracranial neoplasm, arteriovenous malformation, or aneurysm Arterial puncture at noncompressible site within 1 wk Current SBP > 185 mm Hg or DBP > 110 mm Hg Current use of anticoagulant agents with evidence of elevated sensitive laboratory tests, including direct-acting oral anticoagulants and therapeutic doses of low-molecular-weight heparin **Additional exclusion criteria for 3- to 4.5-hr window:** NIHSS > 25 Current treatment with PO anticoagulants (regardless of INR) Evidence of ischemic injury > 1/3 of MCA territory

[a] Exclusions are primarily based on the risk of systemic bleeding or hemorrhagic conversion of stroke.

DBP = diastolic blood pressure; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale (score); SBP = systolic blood pressure; tPA = tissue plasminogen activator.

Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:581-641. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-e99. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344-e418.

   2. Permissive hypertension
      a. Reduction in blood pressure after thrombolysis or recanalization is reasonable within the first 24 hours after the onset of stroke.

- b. Reduce blood pressure cautiously to avoid hypotension or underperfusion of infarcted area (less than 15% blood pressure lowering).
- c. Resumption of home blood pressure medications is reasonable 24 hours after the onset of stroke.
- d. Recommended to treat blood pressure in patients who do not receive thrombolytics if it exceeds SBP greater than 220 mm Hg or DBP greater than 120 mm Hg

3. Seizure prophylaxis. Use of anticonvulsant medications for seizure prophylaxis is not indicated after ischemic stroke.
4. Mechanical thrombectomy and neuroendovascular interventions for ischemic stroke
   - a. Neuroendovascular devices may be used to remove or disrupt clot to facilitate recanalization.
   - b. No difference in safety outcomes when comparing usual care with usual care plus mechanical thrombectomy
5. Many clinical trials support mechanical thrombectomy in patients with acute ischemic stroke.
   - a. Increases the likelihood of independence or improved modified Rankin Scale score compared with standard therapy
   - b. Does not increase the risk of intracerebral hemorrhage (ICH)
   - c. Extends the treatment window to 24 hours after last known well for both patients receiving tissue plasminogen activator (tPA) within the therapeutic window and those who are ineligible for tPA if they meet selection criteria
6. Blood pressure management after thrombectomy
   - a. Current literature suggest that intensive blood pressure lowering should be avoided following thrombectomy. The conventional target systolic BP of 140–180 mm Hg appears reasonable following successful thrombectomy and is associated with better outcomes following thrombectomy (Mistry 2023; Nam 2023).
7. Secondary prevention
   - a. Initiating aspirin (325 mg × 1; then 81–325 mg/day), a high-intensity statin, and an intensive blood pressure regimen is necessary.
     - i. Ideally, give as soon as feasible after the onset of stroke.
     - ii. Aspirin should not be initiated within 24 hours of alteplase.
   - b. Clopidogrel 75 mg daily is also an option in patients whose aspirin therapy has failed or who have an aspirin allergy.
   - c. Aggrenox (dipyridamole/aspirin) and ticagrelor plus aspirin (less than 100 mg) are also effective alternatives to aspirin for secondary prevention.
   - d. Control/modification of other disease states is often necessary.
   - e. Hypertension: typical blood pressure goal is less than 130/80 mm Hg (Stroke 2021;52:e364-467).
   - f. Atrial fibrillation
     - i. Rate or rhythm control
     - ii. Anticoagulation (warfarin, direct-acting oral anticoagulants)
     - iii. Typically, anticoagulant therapy is delayed until at least 5–14 days after stroke to reduce the risk of hemorrhagic conversion.
     - iv. Avoid using loading doses of warfarin.
   - g. Carotid artery stenosis: Stent versus endarterectomy (usually for patients with greater than 70% blockage and/or clinically evident symptoms)
     - i. Aspirin 81–325 mg daily after endarterectomy
     - ii. Dual antiplatelet therapy should be given for 3 months if stent placement is required, followed by one antiplatelet agent thereafter.
   - h. Control of diabetes (blood glucose 140–180 mg/dL)
   - i. Identification and treatment of inherited or acquired hypercoagulable states

VIII. INTRACEREBRAL HEMORRHAGE

A. Epidemiology. Around 50,000 cases in the United States annually
  1. Diagnosis/pathogenesis
    a. Neurologic examination
    b. Vital signs
    c. NIH Stroke Scale and/or GCS score
  2. Imaging and other tests
    a. CT or MRI scan of the brain
    b. CT angiography or contrast-enhanced CT (to help identify patients at risk of hematoma expansion and to evaluate for underlying structural lesions)
    c. Medication history to identify agents that might produce coagulopathy
    d. Laboratory tests
    e. Blood glucose
    f. INR
    g. CBC

B. Causes
  1. Chronic/poorly treated hypertension
  2. Oral anticoagulant use
  3. Cocaine/other stimulant use
  4. Ischemic stroke with hemorrhagic transformation
  5. Chronic alcohol intake
  6. Brain tumor
  7. Arteriovenous malformation
  8. Amyloid angiopathy

C. Clinical Impact – Death or major disability occurs in around 50% of patients.

D. Treatment Considerations (Stroke 2015;46:2032-60)
  1. Anticoagulant reversal
    a. Prompt anticoagulant reversal is necessary. Reversal of laboratory values does not mean that hemostasis will occur in all cases, especially with the newer oral anticoagulants (Table 11).
    b. rFVIIa is not recommended for reversal of anticoagulation because it only replaces one clotting factor and does not appear to be effective for dabigatran reversal. However, if no other reversal agents are available, rFVIIa may be an option for patients who cannot accept human blood products.
  2. Reversal of antiplatelet agents is somewhat controversial.
    a. Two prospective studies suggest that platelet transfusion for patients taking antiplatelet agents with a new ICH is harmful (Lancet 2016;387:2605-13; J Neurosurgery 2013;118:94-103).
      i. Both studies included patients with a small, stable ICH. Primarily basal ganglia hemorrhages, which are traditionally nonoperative
      ii. Patients receiving dual antiplatelet therapy were underrepresented in both studies.
    b. Routine administration of platelet transfusion for any patient with ICH who took antiplatelet agents before admission is not advisable.
    c. Platelet transfusion is likely still indicated for patients who:
      i. Have an urgent need for surgery or a ventriculostomy and have abnormal platelet function tests (if available)
      ii. Have a large ICH, receiving antiplatelet agents and requiring neurosurgery
      iii. Have acute neurologic decline with an intracranial hemorrhage

Table 11. Anticoagulant Reversal Options

Anticoagulant	Reversal Agent and Dose	Adverse Effects
Warfarin	4F-PCC [INR < 4 (25 units/kg, max 2500 units), INR 4–6 (35 units/kg, max 3500 units), INR > 6 (50 units/kg, max 5000 units)] + vitamin K 10 mg IV Alternative: FFP 10–15 mL/kg + vitamin K 10 mg IV	Thrombosis, anaphylactoid reaction, (vitamin K), pulmonary edema, or transfusion-related reaction (FFP), contains heparin (4F-PCC)
PO factor Xa inhibitors (rivaroxaban, apixaban)	Andexanet alfa (Andexxa) (see dosing information that follows in Table 12) or 4F-PCC 25–50 units/kg or activated 4F-PCC (FEIBA) 25–50 units/kg	Andexanet Thrombosis; limited data for reversal, especially with FEIBA
PO DTIs[a] (dabigatran)	Idarucizumab (Praxbind) 5 g IV × 1; repeat dose may be necessary in patients with high DTI exposure or poor renal function	Thrombosis; limited data analyses show minimal efficacy for reversal with PCC and FEIBA
PO antiplatelets	Platelet transfusion infusion (usefulness is uncertain – see Neurocrit Care 2016;24:6-45) Consider desmopressin 0.4 mcg/kg IV	Pulmonary edema or transfusion-related reaction
Unfractionated heparin	Protamine 1 mg (max 50 mg) for each 100 units of heparin (infused within the past 2–3 hr)	Hypotension, hypersensitivity
Low-molecular-weight heparins	Protamine 1 mg (max 50 mg) for each 1 mg of enoxaparin (within 8 hr of last dose)	Hypotension, hypersensitivity

[a]Reversal options have not been tested in patients with ICH and have had varying degrees of coagulopathy reversal in experimental animal and human models.

DTI = direct thrombin inhibitor; FEIBA = factor eight inhibitor bypassing activity; FFP = fresh frozen plasma; 4F-PCC = 4-factor prothrombin complex concentrate.

Table 12. Andexanet Alfa Dosing Based on Factor Xa Inhibitor Dose

Factor Xa Inhibitor	Last Dose	< 8 hr or Unknown Since Last Dose	≥ 8 hr Since Last Dose
Apixaban	≤ 5 mg > 5 mg or unknown	Low dose High dose	Low dose
Rivaroxaban	≤ 10 mg > 10 mg or unknown	Low dose High dose	

Low dose = 400 mg at a target rate of 30 mg/min, then 4 mg/min for up to 120 min; high dose = 800 mg at a target rate of 30 mg/min, then 8 mg/min for up to 120 min.

3. Blood Pressure Management
   a. Prompt control of blood pressure is essential.
   b. Historically, caution may have been used in rapidly reducing blood pressure in patients with chronic hypertension because of concerns regarding accommodations in cerebral autoregulation.
   c. However, there may be some benefit of rapidly reducing the blood pressure to approximately 140-150 mm Hg (and thus reducing the risk of hemorrhage expansion). This may outweigh concern for cerebral autoregulation issues and potential for ischemia, but patients with initial SBP >180 mm Hg may have a greater risk of renal dysfunction.
   d. INTERACT-2 – Large, prospective, randomized trial that compared blood pressure control within 1 hour (N Engl J Med 2013;368:2355-65). SBP less than 140 mm Hg was as safe and effective as SBP less than 180 mm Hg (and may have improved functional outcomes).
   e. ATACH-2 – Large, prospective, randomized trial comparing blood pressure control within 4½ hours in patients with SBP >180 mm Hg. Targeting an SBP goal of 110–139 mm Hg was as effective as targeting an SBP goal of 140–179 mm Hg but was associated with increased renal adverse events at 3 months. (Mean minimum SBP in the first 2 hours after randomization was 128.9 mm Hg in the intensive-treatment group and 141.1 mm Hg in the standard-treatment group.) (N Engl J Med 2016;375:1033-43).

f. Evidence also suggests that blood pressure fluctuations in the first 4–6 hours post-ICH are associated with poor functional outcomes (Stroke 2018;49:348-54).

g. Large, international, multicenter, stepped-wedge cluster randomized trial aimed at assessing the effect of a goal-directed care bundle on functional outcomes in patients with acute intracerebral hemorrhage. The bundle, which included intensive blood pressure control (target less than 140 mm Hg), glucose management, antipyrexia, and rapid anticoagulation reversal, was implemented within 6 hours of symptom onset. The care bundle group demonstrated a favorable shift in functional outcomes on the modified Rankin Scale (mRS) at 6 months, with a common odds ratio of 0.86 (95% CI, 0.76–0.97; P = .015) compared with the usual care group, suggesting improved recovery. A significant portion of the effect size was attributed to intensive blood pressure control, with patients in the care bundle group also experiencing fewer serious adverse events (16.0% vs 20.1%; P = .0098) (Lancet 2023; 402(10395):27-40).

4. Seizure Prophylaxis. Use of anticonvulsants for seizure prophylaxis is not indicated after ICH.
5. VTE prophylaxis should be initiated about 24 hours after symptom onset or surgical evacuation.

Patient Case

Questions 3 and 4 pertain to the following case.
A 61-year-old man is admitted with acute onset of difficulty speaking, confusion, and right-sided weakness. His NIH Stroke Scale score is 20. A head CT scan reveals a right parietal intracerebral hemorrhage (ICH). The patient's home medications include hydroxychloroquine, ibuprofen as needed, warfarin, amlodipine, and donepezil. His medical history includes a deep venous thrombosis (1 year ago), hypertension, early dementia, and arthritis. Serum laboratory values include Na 140 mEq/L, K 3.6 mEq/L, BUN 27 mg/dL, SCr 1.8 mg/dL, glucose 289 mg/dL, Hct 36.7%, Plt 245,000/mm^3, and INR 6.8. His vital signs include blood pressure 163/101 mm Hg, heart rate 99 beats/minute, Sao_2 97%, and respiratory rate 20 breaths/minute.

3. Which is the most appropriate initial therapy in addition to vitamin K for this patient's care?
   A. Reinitiate amlodipine.
   B. Give 4-factor prothrombin complex concentrate (4F-PCC) 50 units/kg intravenously × 1.
   C. Give 6-pack infusion of platelets.
   D. Give recombinant factor VIIa (rFVIIa) 90 mcg/kg intravenously × 1.

4. For this 61-year-old patient with ICH, which is the most appropriate initial antihypertensive therapy?
   A. Clevidipine 1-mg/hour infusion to keep SBP 180 - 220 mm Hg.
   B. Nicardipine 5-mg/hour infusion to keep SBP 140 - 150 mm Hg.
   C. Labetalol 10 mg intravenously as needed to keep SBP 160 - 200 mm Hg.
   D. Esmolol 50-mcg/kg/minute infusion to keep SBP 120 - 130 mm Hg.

IX. SUBARACHNOID HEMORRHAGE

A. Epidemiology
   1. Occurs in around 11.4 per 100,000 person-years. Worldwide incidence is around 6.1 per 100,000 person-years.
   2. 60%–70% female, typical age 40–60 years

B. Diagnosis/Pathogenesis
  1. Serial neurologic examination
  2. Vital signs
  3. NIH Stroke Scale and/or GCS score

Table 13. SAH Severity Scale Scores

	Score Range	Comments
Hunt and Hess	0 (no symptoms) to 5 (moribund)	Best correlated with risk of mortality
World Federation of Neurological Surgeons	1 (GCS score 15, no deficit) to 5 (GCS score 3–6)	Integrates risk of mortality and motor dysfunction
Fisher	1 (no blood visualized) to 4 (diffuse SAH, ICH, or intraventricular hemorrhage present)	Best correlated with risk of vasospasm

C. Imaging (Stroke 2023;54:314-70)
  1. CT scan of brain
  2. Lumbar puncture when CT scan of brain is negative for blood
  3. Digital subtraction (“conventional”) angiography
  4. May use CT angiography or magnetic resonance angiography if conventional angiography is unavailable
  5. Transcranial Doppler, often daily during peak vasospasm risk period

D. Medication History – To identify agents that might produce coagulopathy or hypertension

E. Laboratory and Other Tests
  1. INR
  2. CBC
  3. Troponin
  4. ECG (electrocardiogram)
  5. Echocardiogram

F. Causes – Typically caused by cerebral aneurysm. Modifiable risk factors for SAH:
  1. Hypertension
  2. Smoking
  3. Illicit drug use

G. Clinical Impact
  1. Sudden death: Around 22%–26% of patients die before hospitalization. Inpatient mortality 13.1% in 2018 (United States).
  2. Vasospasm and delayed ischemic neurologic deficits
    a. Presence of blood in subarachnoid space elicits a chemical meningitis-type inflammatory response and results in hemolysis of subarachnoid blood.
    b. Vasospasm (persistent vasoconstriction) occurs, reducing distal cerebral blood flow.
      i. Typical course is 3–14 days, but can occur out to 21 days post ictus.
      ii. Vasospasm risk peaks at around 7–10 days.
    c. Several mechanisms of pathogenesis
      i. Inflammatory infiltration

      - ii. Endothelin activation
      - iii. Liberation of hemoglobin results in the scavenging of nitric oxide.
    - d. Vasospasm is one of the main factors resulting in death or disability after an acute SAH, aside from initial ictus.

- H. Treatment Considerations (Stroke 2023;54:314-70)
  - 1. Surgical management to prevent rebleeding and 'secure' aneurysm
    - a. Craniotomy and aneurysm clipping
    - b. Endovascular aneurysm coiling
  - 2. Agents for preventing vasospasm or delayed ischemic neurologic deficits
    - a. Nimodipine (Br Med J 1989;298:636-42)
      - i. Is a "cerebrovascular-specific" lipophilic dihydropyridine calcium channel blocker
      - ii. 60 mg orally or by tube every 4 hours × 21 days (dose reduction 30 mg every 2 hours may be considered if 60 mg dose intolerable): The clinical impact of dose reducing or discontinuing nimodipine because of hypotension is not well understood but may be associated with unfavorable outcomes (Neurocrit Care 2016;25:29-39).
      - iii. Only U.S. Food and Drug Administration (FDA) label-approved medication to reduce delayed ischemic neurologic deficits associated with SAH
      - iv. Clinical trials did not show a large effect of nimodipine on the occurrence of vasospasm (though the incidence of delayed ischemic neurologic deficits were significantly less).
      - v. Possibly neuroprotective
      - vi. Administration issues in patients who require enteral doses – Black box warning against inadvertent intravenous administration if nursing staff extract nimodipine from the gel capsule at the bedside.
      - vii. Nursing should be prohibited from extracting the gel inside the nimodipine capsule for bedside administration (may increase the risk of inadvertent intravenous administration, incomplete extraction from the capsule) (Neurocrit Care 2015;22:89-92).
      - viii. There is a commercially available liquid product that is for use in patients with swallowing difficulty or feeding tubes. Pharmacy compounding of nimodipine syringes from liquid capsules has been reported but further studies are warranted to determine the optimal enteral formulation. (Pharmacotherapy 2023;43:279-90).
    - b. Antifibrinolytic agents
      - i. Use of antifibrinolytic agents such as aminocaproic acid or tranexamic acid has been evaluated after SAH.
      - ii. Older data analyses before the advent of endovascular interventions suggested that rebleeding is less common with these agents (primarily aminocaproic acid) but that stroke may be more common.
      - iii. More recent data analyses suggest that a short infusion (less than 72 hours) reduces rebleeding but probably does not affect long-term outcomes.
        - (a) The 2023 American Heart Association SAH guidelines moderately support this strategy in early SAH management (Stroke 2023;54:314-70)
        - (b) For example, use of 1000 mg of tranexamic acid intravenously every 6 hours until the aneurysm is secured
    - c. Statins
      - i. Preservation of nitric oxide balance as heme is liberated during SAH hemolysis.
      - ii. Phase II data with pravastatin and simvastatin
      - iii. Phase III trial (STASH) showed no benefit of applying statins in aneurysmal SAH (Lancet Neurol 2014;13:666-75).

        - iv. Abrupt withdrawal of statins in patients who were taking statins before SAH may result in a withdrawal effect and increase the risk of vasospasm.
    - d. Other studied agents
        - i. Magnesium – No usefulness in attaining magnesium concentrations 3–4 mEq/L. Maintaining magnesium at normal concentrations (i.e., preventing hypomagnesemia) is advisable.
        - ii. Clazosentan – No usefulness in blocking endothelin-1
        - iii. Albumin – Not beneficial and may be associated with an increase in pulmonary edema
3. Treatment of vasospasm
    - a. Intra-arterial therapies (see Table 14)
    - b. Triple-H therapy (hypertension, hypervolemia, hemodilution)
        - i. No longer recommended in the traditional format. Euvolemia is better than hypervolemia – Similar outcomes in clinical trials, less pulmonary edema
        - ii. Hemodilution has not been shown beneficial.
    - c. Hyperperfusion therapy
        - i. Better descriptor for the goal of therapy
        - ii. Vasospasm causes distal vasoconstriction to the point of ischemia.
        - iii. Maximizing cerebral blood flow mitigates ischemia.
    - d. Contemporary therapy includes:
        - i. Euvolemia
        - ii. Vasopressors (blood pressure targets are ill defined, but are also typically patient- and symptom-dependent)
        - iii. Inotropes (milrinone)
        - iv. Superselective intra-arterial vasodilators (e.g., verapamil, nicardipine)
4. Headache
    - a. “Worst headache of my life” is the typical chief concern for an aneurysmal SAH.
    - b. Multimodality treatment will be needed to improve patient satisfaction during hospital admission (which may be up to 14–21 days).
    - c. Optimal choice of agents is not well known.
        - i. Common analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (if aneurysm is secured)
        - ii. Other therapies such as magnesium, corticosteroids, or gabapentin may be helpful.
        - iii. Agents that contain caffeine are often used for headache but may not be appropriate, given the risk of cerebral vasospasm after SAH.
        - iv. Opioids may be needed, but use should be limited to avoid sedation and inability to monitor neurologic examination.
        - v. Nonpharmacologic therapies like warm compresses on the back of the neck, minimization of noise, and minimization of bright light may also be useful.
5. Seizure prophylaxis (Stroke 2023;54:314-70)
    - a. Use of anticonvulsants for seizure prophylaxis is controversial after SAH.
    - b. For new-onset seizures after aSAH, treatment with antiseizure medication for 7 days is recommended.
    - c. Prophylactic antiseizure medication should not be routinely used but can be considered in high-risk patients (with ruptured middle cerebral artery aneurysm, ICH, high-grade aSAH, hydrocephalus, or cortical infarction).
    - d. Phenytoin use is associated with excess morbidity and should be avoided.

6. Role of nicotine replacement therapy (NRT) – Smoking is a common risk factor for developing cerebral aneurysms.
    a. Nicotine administration to naive users causes vasoconstriction, whereas administration to heavy users causes little reaction. Nicotine withdrawal in heavy users causes acute, temporary vasodilation, which may lead to headaches.
    b. Seder et al.: Neurocrit Care 2011;14:77-83: Evaluated safety of NRT in active cigarette smokers admitted with an aneurysmal SAH and included 128 who received NRT and 106 who did not. Despite its vasoactive properties, NRT administered among active smokers with acute aneurysmal SAH appeared safe, with similar rates of vasospasm and delayed cerebral ischemia and a slightly higher rate of seizures.
    c. Panos et al.: Am J Health Syst Pharm 2010;67:1357-61: No difference in unfavorable discharge disposition among neurosurgery ICU patients who were smokers treated with NRT (n=114), smokers not treated with NRT (n=113), and nonsmokers not treated with NRT (n=113). Primary admitting diagnosis for neurosurgery patients included SAH, ICH, other trauma, and elective neurosurgery.

X. INTERVENTIONAL ENDOVASCULAR MANAGEMENT

A. Intra-arterial Therapies (Pharmacotherapy 2010;30:405-17)
    1. Administration technique -- typically administered during cerebral angiography
    2. Catheter advanced to vessels with lesion/vasospasm, and drug is infused locally (“superselective infusion”)

B. Vasodilators
    1. Calcium channel blockers
        a. Typically used for cerebral vasospasm associated with SAH
        b. Direct, local infusion typically results in immediate vasodilation.
        c. Usually effective in proximal and distal vessels
    2. A trial is ongoing to determine the optimal intra-arterial drug treatment regimen (nicardipine vs. verapamil vs. nicardipine plus verapamil plus nitroglycerin) for arterial lumen restoration post-cerebral vasospasm after aneurysmal SAH (Intra-arterial Vasospasm Trial at https://clinicaltrials.gov/ct2/show/record/NCT01996436).

Table 14. Typical Agents for Intra-arterial Use for Cerebral Vasospasm

Agent	Typical Dose	Adverse Effects
Nicardipine	2–25 mg, up to 5 mg/vessel	Systemic hypotension Increased ICP
Verapamil	1–10 mg	Systemic hypotension Bradycardia Increased ICP
Milrinone	5–15 mg	Systemic hypotension

ICP = intracranial pressure.

C. Intra-arterial Thrombolysis
    1. Most often used in patients with ischemic stroke
    2. Limited evidence to support combining with intravenous thrombolytic as a standard of care
    3. Current roles

  - a. Combination with mechanical thrombectomy
  - b. Rescue therapy in patients having received intravenous thrombolytic
  - c. Large hemispheric infarction
    - i. Dose is not well defined.
    - ii. Typically applied until thrombus has resolved
    - iii. Alteplase dose less than 20 mg

Patient Case

Questions 5 and 6 pertain to the following case.
A 49-year-old woman presents to an urgent treatment center with the "worst headache of her life." She is sent to your emergency department, where a head CT scan reveals a diffuse SAH. The patient takes no home medications and has an insignificant medical history other than a 20 pack-year history of smoking.

5. Which therapy is most appropriate to prevent ischemic complications from SAH?
   - A. Nimodipine for 21 days.
   - B. Euvolemia and permissive hypertension for 14 days.
   - C. Simvastatin for 14 days.
   - D. Aminocaproic acid infusion for 48 hours.

6. On hospital day 5, the patient has reduced alertness, and her GCS score decreases by 2 points. The digital subtraction angiography suggests cerebral vasospasm. Which treatment modality is best to initiate first?
   - A. Norepinephrine 0.05 mcg/kg/minute to increase MAP to 90 mm Hg.
   - B. One unit of packed RBCs to increase Hgb to 10 g/dL.
   - C. 3% sodium chloride boluses to increase central venous pressure to 14 mm Hg.
   - D. Milrinone 0.375-mcg/kg/minute infusion to increase cardiac index to 5 L/minute/m^2.

D. Stent Deployment and Antiplatelet Agents
  1. Intracranial stents are often deployed in place of coils or to support coils for complex aneurysms.
  2. Intracranial circulation is different from coronary circulation.
     - a. Blood vessels are generally smaller and more tortuous.
     - b. Flow rate is lower.
     - c. Epithelialization of stent takes longer.
  3. Dual antiplatelet therapy is typically used around the time of stent placement.
     - a. Clopidogrel (a prodrug) plus aspirin
     - b. Current evidence suggests therapy for up to 3 months (not 4 weeks like after percutaneous coronary intervention), followed by aspirin monotherapy thereafter.
     - c. Platelet testing may be necessary in some individuals to evaluate their pharmacogenetic response to clopidogrel.
     - d. No gold standard for platelet reactivity testing in this setting. VerifyNow is commonly used and measures platelet reactivity units (PRU) for aspirin and P_2Y_{12} inhibitors.
     - e. Some patients may not respond to clopidogrel (up to 30%), and additional loading doses and increased maintenance doses are not effective.
     - f. Ticagrelor may play a role in patients with a variable response to clopidogrel (must be used in combination with aspirin less than 100 mg) (Neurocrit Care 2024;40:262-71).
     - g. Prasugrel (a prodrug) is not recommended (unless absolutely necessary) in patients with high on-treatment platelet reactivity (e.g. clopidogrel non-responders) because of warnings about use in patients with a history of stroke – Increased bleeding. Reduced doses (2.5–5 mg) have been reported with some success in preventing thrombosis without excessive bleeding.

Patient Case

Questions 7 and 8 pertain to the following case.
A 52-year-old woman is admitted to your ICU after a single-vehicle crash. She has many orthopedic injuries to her lower extremities and a subdural hematoma, which will require an emergency craniotomy for evacuation. Her home medications include metoprolol, rivaroxaban 10 mg (last dose 5 hours ago), lisinopril, and atorvastatin. Her medical history is significant for atrial fibrillation. Laboratory values on admission were notable for Hct 31.2% and Plt 577,000/mm^3.

7. Which laboratory test would have the capability of assessing whether or not the patient was taking their rivaroxaban?
   A. INR.
   B. Anti-Xa activity concentration.
   C. Activated partial thromboplastin time.
   D. VerifyNow PRU test measurement.

8. Which therapy would be most appropriate to reverse rivaroxaban before this patient's emergency craniotomy?
   A. 4F-PCC 50 units/kg intravenously × 1.
   B. Andexanet 200 mg intravenously x 1.
   C. Fresh frozen plasma 15 mL/kg intravenously × 1.
   D. rFVIIa 90 mcg/kg intravenously × 1.

XI. ACUTE SPINAL CORD INJURY

A. Epidemiology – Annual incidence of 15–40 cases per 1 million people in the United States

B. Diagnosis/Pathogenesis
   1. Diagnostic tests
   2. Neurologic examination
      a. The American Spinal Injury Association (ASIA) Impairment Scale is a helpful guide to understanding an injury. It was developed by doctors at the ASIA to categorize the extent of an injury in terms of the degree of damage to the spinal cord. If the injury is "complete," (ASIA A) it means that no messages can travel across the location of the injury to the brain. However, "incomplete" injuries, which mean that some messages can still transmit, are classified as ASIA B, ASIA C, or ASIA D, depending on amount of movement and feeling that remain below the level of the injury. The classifications are as follows:
         i. ASIA A: Complete, no motor or sensory function is preserved below the level of the injury, including the sacral segments S4–S5
         ii. ASIA B: Incomplete Sensory, but no motor function is preserved below the neurological level of injury, and includes the sacral segments S4–S5
         iii. ASIA C: Incomplete, motor function is preserved below the neurological level of injury, but more than half of the key muscles below the level have a muscle grade less than 3 (i.e., unable to move against gravity)

        iv. ASIA D: Incomplete, motor function is preserved below the neurological level of injury, and at least half the key muscles below the injury level have a muscle grade of 3 or more (i.e., joints can be moved against gravity)
        v. ASIA E: Normal, motor and sensory functions are normal

C. Imaging (Neurosurgery 2013;60(suppl 1):82-91)
    1. CT scan of spine
    2. Many views of spine radiography are necessary when a CT scan is unavailable.

D. Causes
    1. 40%–50% are caused by motor vehicle collisions.
    2. Falls (20%), violence (14%), recreational and work activities

E. Clinical Impact
    1. Mortality
        a. 50%–75% at the time of injury
        b. Hospital mortality 4.4%–16%
    2. Morbidity
        a. Paralysis and loss of sensation
        b. Spasticity
        c. Orthostatic hypotension
        d. Autonomic dysreflexia
        e. VTE
        f. Decubitus ulcers
        g. Respiratory insufficiency
        h. Bowel and bladder dysfunction
        i. Sexual dysfunction
        j. Treatment considerations
        k. Neurogenic shock
            i. Hypotension often occurs after injury (50%–90% of cervical spine injuries).
            ii. May be associated with malperfusion of the spinal cord and worsened outcomes
            iii. Etiology of shock is decreased sympathetic nervous system outflow. Continues to be counterbalanced by parasympathetic outflow, which is not affected by SCI
            iv. Results in hypotension and bradycardia

F. Blood Pressure Management
    1. Typical recommendations after an acute SCI are to maintain MAP 85–90 mm Hg for 7 days to ensure adequate spinal perfusion.
    2. Little high-quality evidence supports this recommendation, but the recommendation is included in the SCI guidelines as a treatment option.
    3. Often requires judicious fluid resuscitation and vasopressor support
    4. Persistent hypotension may be treated with fludrocortisone or midodrine.
    5. Persistent bradycardia may be treated with pseudoephedrine or low-dose theophylline.
    6. Droxidopa, an enteral analog of norepinephrine, may be useful for blood pressure augmentation in this setting.

G. VTE Prophylaxis
    1. VTE occurs in 80%–100% of patients without pharmacologic prophylaxis

2. Low-molecular-weight heparins are the drugs of choice for prophylaxis and should be initiated within 36 hours post-injury.
3. Duration of prophylaxis is typically about 8 weeks.

H. Role of High-Dose Methylprednisolone (Neurosurgery 2013;60(suppl 1)82-91; J Neurosurg 1998;89:699-706; JAMA 1997;277:1597-604; J Neurosurg 1992;76:23-31; N Engl J Med 1990;322:1405-11)
   1. Controversial topic related to NASCIS-II and NASCIS-III trials
   2. Methylprednisolone 30 mg/kg intravenously × 1, followed by 5.4 mg/kg/hour within 8 hours of injury for 24 or 48 hours
   3. Both trials suggested a modest benefit in the first 6 weeks or 6 months (which often did not persist at 1 year) and a modest risk (primarily related to infection). Current guidelines do not support administering high-dose methylprednisolone.
   4. NASCIS-II split enrolled population in half (those who received the drug before the median time to administration [8 hours] and those who did not).
      a. Subgroup analysis may not have been powered to show benefit.
      b. Reported motor and sensory scores from one side of the body, not both. The investigators later said there was no difference but have not allowed others to examine the raw data.
   5. Consistently showed risk (GI bleeding, infection) and inconsistently showed benefit
   6. Potential treatment effects may have been caused by early surgery or additional benefit of high-dose methylprednisolone therapy in combination with early surgery.
   7. NASCIS-III used a functional independence measure (FIM) score to show how improvement in muscle strength might translate to improved outcomes. Failed to show a difference in FIM score
   8. If a practitioner does choose to use high-dose steroids in SCI:
      a. Must use methylprednisolone; no other steroids
      b. Must use NASCIS-II or NASCIS-III dosing
      c. Must give within 8 hours of injury

XII. BRAIN TUMORS

A. Epidemiology
   1. According to the National Brain Tumor Society, an estimated 94,000 Americans received a new primary brain tumor diagnosis in 2023. Primary brain tumors (from brain cells such as meninges and neural tissues)
      a. Glioblastoma
      b. Meningioma
      c. Pituitary adenoma
      d. Astrocytoma
   2. Brain metastases – Common neoplasms that result in spread to brain
      a. Lung (40%–50%)
      b. Breast (15%–20%)
      c. Melanoma (5%–10%)
      d. Colon (4%–6%)
      e. Renal cell carcinoma
      f. CNS lymphoma

B. Diagnosis/Pathogenesis – Diagnostic tests
  1. Contrast-enhanced MRI is the most common test.
  2. Biopsy is often necessary to reveal the specific histology.

C. Clinical Impact – Mortality is often high, depending on the type and grade of the tumor.

D. Treatment Considerations
  1. Corticosteroids for brain edema
    a. Dexamethasone commonly used for vasogenic edema associated with tumors
      i. Reduces peritumoral edema and symptoms associated with increased ICP. Temporarily reduces symptoms (neurologic dysfunction, seizures, headache)
      ii. Dose is commonly 4 mg intravenously every 6 hours.
      iii. May use other corticosteroids at comparable doses
    b. Use of acid-suppressive agents (famotidine) may help with concomitant steroid use to reduce the risk of GI complications (Wien Med Wochenschr 1988;138:97-101).
    c. Consideration for glycemic control
    d. Induction of phenytoin metabolism (because of increased metabolic rate)
    e. Metabolism induced by phenytoin (because of increased cytochrome P450 [CYP] activity)
  2. VTE prophylaxis and treatment
    a. High risk of VTE
    b. Consider using combination pharmacologic/mechanical prophylaxis.
    c. Enoxaparin is superior to warfarin for the treatment of VTE in oncology patients.
  3. Seizure prophylaxis
    a. Not typically indicated
    b. Around 50% of patients with primary brain tumor present with seizure, which must be treated with anticonvulsant medications.
    c. Phenytoin, carbamazepine, and levetiracetam are often recommended; however, caution should be used with agents that have been associated with Stevens-Johnson syndrome/toxic epidermal necrolysis (e.g., phenytoin, carbamazepine) in patients who also require radiation therapy.
    d. Hepatic CYP enzyme-inducing agents, including phenytoin, should be used with caution because of possible drug interactions with chemotherapy.

XIII. CRITICAL ILLNESS POLYNEUROPATHY

A. Epidemiology
  1. Exact incidence is unknown because of inconsistent monitoring and diagnosis.
  2. May be as high as 60% in patients with acute respiratory distress syndrome, 77% in long ICU stay (greater than 7 days), 80% in patients with multiorgan failure

B. Diagnosis/Pathogenesis – Diagnostic tests
  1. Typically suspected when patients do not wean well from the ventilator or if their limbs are weak/flaccid
  2. Electrophysiologic studies or muscle biopsy may provide a more precise diagnosis. Differential diagnosis includes evaluation for critical illness myopathy, Guillain-Barré syndrome, electrolyte abnormalities

C. Causes
  1. The cause of critical illness polyneuropathy is unknown, but several hypotheses exist.
    a. Mitochondrial dysfunction in critical illness may cause energy stress in vulnerable neurons.

    b. Microcirculatory ischemia
    c. Protein catabolism in severe critical illness/immobility may cause muscle wasting.
2. Often associated with:
    a. Sepsis
    b. Multiorgan dysfunction
    c. Hyperglycemia
    d. Renal failure
    e. Neuromuscular blockade
    f. Duration of vasopressor or corticosteroid therapy
    g. Duration of ICU stay

D. Clinical Impact
1. Limb and diaphragm weakness may persist for weeks to months.
2. About 33% of patients with critical illness polyneuropathy ultimately cannot independently ambulate or breathe.

E. Treatment Considerations
1. No specific treatments have been shown effective.
2. Intravenous immunoglobulin may play a role (Lancet Neurol 2008;7:136-44).
3. Intensive glycemic control may reduce critical illness neuropathy.
4. Passive mobilization/early physical therapy in the ICU
5. Daily awakening/less time on the ventilator
6. Limiting risk factors as much as possible

XIV. GUILLAIN-BARRÉ SYNDROME

A. Epidemiology
1. 1.11 cases per 100,000 person-years
2. Men > women (almost 2:1)

B. Diagnosis/Pathogenesis – Diagnostic tests
1. Bilateral symmetric progressive weakness of limbs
2. Generalized hyporeflexia or areflexia
3. Nerve conduction studies may provide a more precise diagnosis.

C. Causes
1. Typically associated with *Campylobacter jejuni* infection. Also associated with Epstein-Barr virus, varicella-zoster, and *Mycoplasma pneumoniae* infections
2. Swine flu vaccine in 1976 caused increased risk of Guillain-Barré syndrome. The same increased risk has not been associated with other seasonal influenza vaccines.

D. Clinical Impact
1. Progressive weakness over 3–4 weeks
2. 20% of patients remain severely disabled.
3. Mortality rate around 5%

4. Respiratory failure
5. Autonomic dysfunction resulting in arrhythmia, hypertension, hypotension
6. Neuropathic pain

E. Treatment Considerations (N Engl J Med 1992;326:1123-9)
   1. Intravenous immunoglobulin versus plasma exchange
      a. Therapies are essentially equivalent.
      b. Plasma exchange: Five treatments over 2 weeks
      c. Intravenous immunoglobulin: 0.4 g/kg intravenously daily × 5 days
      d. Combination of therapies no better than single therapy alone
      e. Benefit of repeated treatments is unclear.
      f. Steroids are not particularly effective.

F. Supportive Care
   1. VTE prophylaxis is imperative.
   2. Careful ventilation strategies to minimize barotrauma and prevent pneumonia
   3. Dysphagia is common, so enteral feeding access is necessary in most cases.
   4. Neuropathic pain is common; use opiates with caution to avoid respiratory depression.
   5. Euvolemia to minimize autonomic instability

XV. MYASTHENIA CRISIS

A. Epidemiology
   1. Annual incidence of myasthenia gravis is 1 or 2 per 100,000.
   2. 15%–20% of patients with myasthenia gravis will develop myasthenia crisis within the first year of illness.

B. Diagnosis/Pathogenesis
   1. Patients with myasthenia crisis typically present with respiratory failure caused by muscle weakness.
   2. Autoimmune disease typically targeting acetylcholine receptors at the neuromuscular junction
   3. Myasthenia crisis is usually preceded by a predisposing factor.
      a. Respiratory infection
      b. Emotional stress
      c. Aspiration
      d. Changes in myasthenia gravis medication regimen
      e. Addition of medications that may oppose acetylcholine effects at the neuromuscular junction and exacerbate myasthenia gravis symptoms (Box 3)
      f. Other physiologic stress (trauma, surgery)

Box 3. Pharmacologic Agents Associated with Myasthenia Crisis

Aminoglycosides	Neuromuscular blockers
β-Blockers	Procainamide
Fluoroquinolones	Quinidine
Macrolides	Tetracyclines
Magnesium	Verapamil

C. Treatment Considerations
   1. Intravenous immunoglobulin 0.4 g/kg/day × 3–5 days or plasmapheresis 20–25 mL/kg plasma × 5 exchanges every other day × 10 days
      a. Similarly effective; can choose according to patient risk factors, etc.
   2. Corticosteroids moderately effective (e.g., prednisone 60–100 mg/d for 2–4 weeks, followed by slow taper)
   3. Supportive Care – Consider discontinuing cholinergic therapies while the patient is acutely ill. May increase pulmonary secretions and complicate ventilator/ICU management

XVI. SEROTONIN SYNDROME

A. Presentation
   1. Autonomic hyperactivity (hypertension, tachycardia)
   2. Mental status changes
   3. Hyperthermia – Diaphoresis
   4. Seizures
   5. Neuromuscular abnormalities
   6. Rigidity
   7. Hyperreflexia and clonus
   8. Shivering
   9. Diarrhea
   10. Generally associated with increased serotonin activity in the central nervous system, which can be caused by a single therapeutic agent, a combination of agents, or overdose. Common serotonergic drugs are listed in Table 15.
   11. Serotonin syndrome presents similarly to Neuroleptic Malignant Syndrome (NMS). Distinguishing features are listed in Table 16.

Table 15. Medications Associated with Serotonin Syndrome

Drug Class	**Associated Drugs**
Antiemetics	Ondansetron, granisetron, metoclopramide
Antiepileptics	Lamotrigine, carbamazepine, valproic acid
Anti-migraine	Triptans, ergotamine, methylergonovine
Herbal products	St. John's wort, tryptophan, ginseng
Illicit drugs	Methamphetamine, amphetamine, ecstasy (MDMA), psilocybin, LSD
Opioids	Fentanyl, meperidine, methadone, dextromethorphan, tramadol[a]
SSRIs	Citalopram,[a] fluoxetine,[a] sertraline,[a] escitalopram, paroxetine
SNRIs	Venlafaxine, duloxetine
TCAs	Amitriptyline, clomipramine, imipramine
MAOIs	Phenelzine, rasagiline, selegiline
Others	Bupropion,[a] buspirone, lithium, trazodone
Miscellaneous	Linezolid, cyclobenzaprine, methylene blue, fluconazole, chlorpheniramine

[a] Top 5 agents implicated in serotonin syndrome

MAOIs = monoamine oxidase inhibitors; SNRIs: serotonin and norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.

Information from: Mikkelsen N, Damkier P, Arnspang Pedersen S. Serotonin syndrome – a focused review. Basic Clin Pharmacol Toxicol 2023;133:124-9; Pedavally S, Fugate JE, Rabinstein AA. Serotonin syndrome in the intensive care unit: clinical presentations and precipitating medications. Neurocrit Care. 2014;21:108-13.

Table 16. Distinguishing Features between Serotonin Syndrome and Neuroleptic Malignant Syndrome.

Feature	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Trigger drug	Drug with serotonergic effect	Drug with dopaminergic effect, often antipsychotics
Onset	Usually within 24 hours	Onset over days to weeks
Remission of symptoms	Rapid remission following discontinuation of the trigger drug	Gradual remission following discontinuation of the trigger drug
Neurologic symptoms	Neuromuscular hyperactivity: tremor, clonus, hyperreflexia	Neuromuscular hypoactivity: Extrapyramidal symptoms, hypokinesia, and lead tube rigidity

Information from: Mikkelsen N, Damkier P, Arnspang Pedersen S. Serotonin syndrome – a focused review. *Basic Clin Pharmacol Toxicol.* 2023;133(2):124-129. https://doi.org/10.1111/bcpt.13912

B. Treatment Considerations
  1. Removal of precipitating drugs/factors – Mild symptoms may resolve in 24–72 hours; if caused by antidepressants, may take weeks to resolve
  2. Control of agitation, seizures, and rigidity – Benzodiazepines
  3. Control of autonomic hyperactivity – Hypotension treatment with direct-acting sympathomimetics
  4. Control of hyperthermia
    a. Cooling blanket
    b. Sedation, neuromuscular paralysis, intubation
    c. Avoid succinylcholine.
  5. Serotonin-2A antagonist blocks serotonin receptors implicated with serotonin syndrome.
    a. Cyproheptadine 12–32 mg/24 hours by mouth or feeding tube. A 12-mg loading dose; then 2 mg every 2 hours as symptoms continue
    b. Chlorpromazine 50–100 mg intramuscularly

XVII. NEUROLOGIC MONITORING DEVICES

A. ICP Monitors
  1. Catheters are typically inserted under sterile conditions at the bedside.
  2. Antibiotic prophylaxis is not useful and should not be used routinely (Neurocrit Care 2016;24:61-81).
  3. Antibiotic-coated catheters are available for patients at high risk of infection.
  4. Temporary catheters
    a. Used primarily in the ICU
    b. Ventriculostomy (a.k.a. external ventricular drain) – Diagnostic and therapeutic
      i. Catheter inserted into frontal horn of lateral ventricle
      ii. Transduces ICP; should be calibrated to zero routinely
      iii. Higher infection rate than with intraparenchymal catheter; insertion is more difficult (particularly with brain swelling)
      iv. Permits drainage of CSF and intraventricular hemorrhage
      v. Permits intraventricular drug administration
    c. Intraparenchymal catheter
      i. Wire that sits in brain tissue
      ii. Transduces ICP
      iii. Low infection rate, fewer complications with insertion

        - iv. Cannot recalibrate the catheter, experience “zero drift” in ICP readings after prolonged use. May not be entirely accurate for duration of use
    - d. Brain tissue oxygen monitor (Licox)
        - i. Intraparenchymal catheter
        - ii. Optimal location of placement is not well defined (injured vs. non-injured tissue).
        - iii. Transduces partial pressure of brain tissue oxygen
            - (a) Goal partial pressure of brain tissue oxygen is usually 25–35 mm Hg.
            - (b) Concept similar to Svo_2 (mixed venous oxygen saturation) values systemically
        - iv. Low values reflect increased ICP or reduced oxygen delivery.
        - v. Typically, will be used in combination with other monitoring modalities
    - e. Subarachnoid bolt
        - i. Single-lumen screw inserted through a burr hole into the subarachnoid space
        - ii. Transduces ICP
        - iii. Associated with increased CNS infection

B. EEG
1. Scalp electrodes are placed externally.
2. Permits evaluation of cortical electrical activity
3. Standard of care for seizure monitoring or if initiating phenobarbital for ICP control to monitor for attainment of burst suppression
4. Newer, less cumbersome devices are currently available that may improve accessibility.
    - a. Point-of-care EEG systems (e.g., Ceribell) may be useful for faster set up and triage of seizures compared with traditional EEG set ups.

C. Transcranial Doppler
1. Ultrasound of intracranial vessels
2. Used in monitoring for cerebral blood flow velocity or vasospasm
3. Threshold values
    - a. 125 cm/second may suggest vasospasm.
    - b. 200 cm/second typically suggests severe vasospasm.
    - c. Lindegaard ratio: Ratio of target blood vessel (usually middle cerebral artery) to carotid (internal carotid artery) blood velocity transcranial Doppler values – value of 3 or more suggests vasospasm

D. Bispectral Index (BIS) Monitor
1. Scalp electrodes are placed externally.
2. Uses EEG information to derive a number; should not be substituted for an EEG in patients with seizures
3. BIS 0–100 (100 being completely wakeful)
4. Little correlation with BIS values and ICP control or extent of pharmacologic coma

E. Pulpilometer
1. A handheld device that uses high-speed camera and computing technology to provide quantitative, reproductible, and precise measurements regarding the pupilary light reflex. This noninvasive technique correlates to ICP and has acceptable accuracy to estimate intracranial hypertension (Robba 2020)
2. The device reports measurements via Neurological Pulp Index derived from a proprietary formula. Values range from 0.0 to 4.9, and a value of less than 3.0 is considered an abnormal or sluggish response.

XVIII. IMPACT OF SOCIAL DETERMINANTS OF HEALTH (SDOH)

A. SDOH are conditions in the places where people live, learn, work, and play that affect health risks and outcomes.

B. Disparates noted in select neurological injuries:
   1. Stroke incidence: Low education, low income, living in an impoverished area, residence in an area with few healthcare services, Southeastern residence, living in rural areas, social isolation, and lacking health insurance
   2. Traumatic brain injury (TBI):
      a. American Indian and Alaska Native have higher rates of TBI-related hospitalizations and deaths compared with other racial or ethnic groups. Factors contributing to this disparity include motor vehicle accidents, substance abuse, and difficulties accessing healthcare.
      b. Military service members saw an increase in TBI because of conflicts from 2005 to 2018
      c. Research suggests almost half of people in correctional or detention facilities have a history of TBI and may face challenges with accessing TBI-related care.
      d. Those who experience homelessness are up to 10 times more likely to have a history of moderate to severe TBI. They have worse overall physical and mental health.
      e. Survivors of intimate partner violence who have experienced a TBI are more likely to be diagnosed with post traumatic stress disorder, insomnia, and depression.
      f. Individuals living in rural areas have a greater risk of death following TBI compared with those living in urban areas because of travel time to receive medical care and less access to Level I Trauma Center.

C. Transportation impact on SDOH
   1. Limited access to transportation can significantly impact patient adherence to medical appointments and medication regimens, ultimately affecting health outcomes (NASEM 2017).

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: C**

Answer C is correct because midazolam (together with lorazepam) is recommended by the status epilepticus guidelines. Answers A, B, and D are incorrect because phenytoin is less effective than lorazepam as the initial agent. Although valproic acid and levetiracetam have not been formally compared with lorazepam as the initial agent for status epilepticus, their use is supported by less clinically rigorous evidence.

2. **Answer: B**

Answer B is correct because clinical evidence supports the safety and efficacy of osmotherapy as a first-line therapy in this situation. Hypertonic saline would be more appropriate than mannitol because of the patient's relatively low serum sodium concentration and elevated SCr (mannitol is cleared renally and is thus not optimal for patients with renal dysfunction, making Answer A incorrect). Answers C and D (pentobarbital and midazolam) are not ideal for this patient because of the likelihood of hypotension.

3. **Answer: B**

Answer B is correct because warfarin is well reversed by 4F-PCC products in a much more timely and complete manner than vitamin K in the acute setting. Answer A is incorrect; although blood pressure control is important for this patient, amlodipine is unlikely to have timely effects immediately after ICH. Answer C is incorrect because platelets are minimally effective for reversing ibuprofen. Answer D is incorrect; rFVIIa is not recommended for reversal of warfarin because of thrombosis risks.

4. **Answer: B**

Answer B is correct because nicardipine is recommended for reducing blood pressure after ICH, and the threshold for treatment is correct according to the INTERACT-2 and ATACH-2 studies. Answer A is incorrect; although clevidipine may be considered in this case, the typical goal blood pressure target after ICH is a SBP 140-150 mm Hg. Answers C and D are incorrect; although labetalol and esmolol also reduce blood pressure, the optimal SBP goal after ICH 140-150 mm Hg.

5. **Answer: A**

Answer A is correct because nimodipine is the only agent with an FDA indication for preventing ischemic complications related to SAH. Answer B is incorrect because prophylactic Triple-H therapy or variants thereof do not prevent ischemic complications; rather, hyperperfusion therapies are used when vasospasm develops. Answer C is incorrect because in clinical trials, the efficacy of statins for preventing vasospasm has failed. Answer D is incorrect because aminocaproic acid may in fact increase the risk of stroke in patients with SAH.

6. **Answer: A**

Answer A is correct because induction of hypertension with a vasopressor such as norepinephrine appears to improve cerebral perfusion. Titrating the infusion to MAP values that result in improved neurologic symptoms is often necessary. Answer B is incorrect because data analyses are limited to support transfusing blood to a high hemoglobin (in fact, blood transfusion appears to be a risk factor for vasospasm). In addition, fluid resuscitation to hypervolemic levels is not beneficial. Answer C is incorrect because when hypervolemia is compared with euvolemia, neurologic outcomes are no different, but patients receiving hypervolemia develop more pulmonary edema. Answer D is incorrect because milrinone is not first-line therapy for vasospasm.

7. **Answer: B**

Answer B is correct because the anti-Xa activity concentration is the laboratory value that best correlates with rivaroxaban activity. Answers A and C are incorrect because neither INR nor activated partial thromboplastin time is typically affected by rivaroxaban alone. Answer D is incorrect because the VerifyNow PRU test measurement is more specific to antiplatelet agents such as aspirin or clopidogrel.

8. **Answer: A**

Answer A is correct because the most consistent reversal effects, although with low-quality evidence, occur with 4F-PCCs. Answer B is incorrect because the appropriate bolus dose of andexanet would be 400 mg followed by a 2-hour continuous infusion, given the dose and time of the last dose. In addition, available data are currently limited regarding the periprocedural use of andexanet. Answer C is incorrect because fresh frozen plasma does not reverse factor Xa inhibitors reliably. Answer D is incorrect; although factor VII may have some usefulness, reversal is incomplete, and factor VII is associated with an increased risk of thrombosis.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: B**

Answer B is correct because sodium supplementation is effective for treating hypovolemic and euvolemic hyponatremia. Although inducing hypervolemia is no longer advocated, ensuring euvolemia is important. Answers A and C are incorrect because water restriction or tolvaptan is undesirable in a patient who is 4 days after ictus for SAH because of the importance of maintaining adequate cerebral perfusion. Hyponatremia may be harmful in a patient with a new stroke such as SAH caused by cerebral edema, making Answer D incorrect.

2. **Answer: A**

Answer A is correct because vancomycin effectively covers MRSE, and the intraventricular dose of 10 mg daily is appropriate. Answer B is incorrect because gentamicin is less likely to be effective alone for MRSE and is more associated with seizures than other aminoglycosides. Answer C is incorrect because ampicillin (or other penicillins) should not be given by the intraventricular route, given the risk of seizures. Answer D is incorrect because this patient has a treatment-refractory, device-related CNS infection. In this instance, intraventricular antimicrobials may be considered.

3. **Answer: B**

Answer B is correct; although the optimal CPP varies with each individual, the typical recommended target range is 60–70 mm Hg. Patients with a TBI have gastric intolerance but benefit greatly from early enteral nutrition, making Answer A incorrect. Answer C is incorrect because dextrose-containing fluids may increase cerebral edema in TBI and lower the serum sodium concentration. Answer D is incorrect because high-dose methylprednisolone therapy increases mortality in patients with a TBI.

4. **Answer: B**

Answer B is correct because this patient meets the criteria for receiving alteplase and has no obvious contraindications. The more timely the alteplase administration, the more likely the patient will benefit (and the less risk). Answer A is incorrect because aspirin should be initiated within the first 24–48 hours after stroke, but not necessarily immediately. Answer C is incorrect because the blood pressure may be slightly elevated (SBP less than 185 mm Hg, DBP less than 110 mm Hg) before alteplase administration or immediately after stroke in general (so-called permissive hypertension to ensure adequate cerebral perfusion). Nicardipine is not necessary for this patient at this point. Answer D is incorrect because reversal of warfarin with vitamin K is not recommended for an acute thrombosis in the brain.

5. **Answer: C**

Answer C is correct; the current guidelines do not recommend high-dose methylprednisolone therapy because of the inconsistency in beneficial effects and the relatively consistent risk of adverse effects (GI bleeding, infection) shown in clinical trials. Answer B is incorrect because high-dose methylprednisolone does not augment spinal perfusion. Answers A and D are incorrect; although the NASCIS-III study showed some potential benefit for patients who received a bolus and a 47-hour infusion when high-dose methylprednisolone therapy was initiated 3–8 hours after injury, particularly for incomplete injuries, the therapy is no longer recommended.

6. **Answer: A**

Answer A is correct; of the agents listed, buspirone is the only one that increases CNS serotonin concentrations. Answers B–D would not be expected to increase CNS serotonin concentrations. Cyproheptadine is a potential therapeutic agent for patients with serotonin syndrome.

7. **Answer: B**

Answer B is correct; given this patient’s change in neurologic status, vital signs, and monitoring values, she is likely having a cerebral vasospasm with increased ICP. Therapy should be targeted at optimizing cerebral perfusion (fluid bolus or increase in MAP) and reducing ICP. Hypertonic saline will address both issues, causing an increase in intravascular volume to improve perfusion and possibly an increase in blood pressure while lowering ICP through osmotic effects. Answer A is incorrect because verapamil must be given superselectively in the angiography suite. One possible adverse effect of verapamil is cerebral vasodilation, which could lead to increased ICP, and ICP would be undesirable in this patient right now. Answer C is incorrect; although mannitol may decrease ICP, it also causes diuresis, which is undesirable in a patient with ongoing cerebral vasospasm. Answer D is incorrect; although a blood transfusion might theoretically increase oxygen-carrying capacity to the brain (enhancing perfusion), a blood transfusion may in fact cause a risk of cerebral vasospasm. In addition, it is unlikely to affect ICP.

8. **Answer: D**

Answer D is correct because propofol is an almost-ideal agent for sedation with its quick onset and offset of activity and relative lack of dependence on organ function for clearance; however, boluses and large dose titrations should be avoided because of the risk of hypotension. Answers A and C are incorrect; long-acting sedating agents such as lorazepam and morphine are undesirable in patients with a neurologic injury because of their propensity to obscure the neurologic examination for prolonged periods. Answer B is incorrect; midazolam (and other benzodiazepines) is associated with increased delirium. In addition, midazolam may accumulate when used for a prolonged period because of its long context-sensitive half-life.

CARDIOVASCULAR CRITICAL CARE I

SAJNI V. PATEL, PHARM.D., BCCP

THE UNIVERSITY OF CHICAGO MEDICINE
CHICAGO, ILLINOIS

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SAJNI V. PATEL, PHARM.D., BCCP

THE UNIVERSITY OF CHICAGO MEDICINE
CHICAGO, ILLINOIS

Learning Objectives

1. Develop an appropriate pharmacotherapeutic regimen based on a patient's hemodynamic status and objective cardiac findings.
2. Design a treatment plan for patients with cardiogenic shock.
3. Develop treatment plans for critically ill patients with cardiovascular diseases, including, but not limited to, coronary artery disease, arrhythmias, heart failure (HF), and valvular disease.
4. Recognize the usefulness of mechanical circulatory support and heart transplantation for patients with advanced HF and cardiogenic shock, as well as the common complications associated with these interventions.

Abbreviations in This Chapter

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome(s)
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CVP	Central venous pressure
DAPT	Dual antiplatelet therapy
ECG	Electrocardiography/electrocardiogram
ECHO	Echocardiography/echocardiogram
ECMO	Extracorporeal membrane oxygenation
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HOCM	Hypertrophic obstructive cardiomyopathy
ICU	Intensive care unit
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MI	Myocardial infarction
NSTEMI	Non–ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PVR	Pulmonary vascular resistance
RV	Right ventricle/ventricular
SA	Sinoatrial
SAM	Systolic anterior motion of the mitral valve
SCAI	The Society for Cardiovascular Angiography and Interventions
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
VAD	Ventricular assist device
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–8 pertain to the following case.

A 58-year-old man (height 71 inches, weight 106 kg) was transferred to the intensive care unit (ICU) from an outlying hospital after 24 hours of progressively worsening chest pain and shortness of breath. He arrives on 6 L of oxygen by high-flow nasal cannula, with a heparin infusion at 16 units/kg/hour and dopamine infusion at 15 mcg/kg/minute. Notes show that he was bradycardic (heart rate of 50–58 beats/minute) and hypotensive (78/49–86/55 mm Hg) on presentation to the outlying hospital. His 12-lead electrocardiogram (ECG) at the outlying hospital showed ST-segment elevation in leads II, III, and aVF. Given his chest pain and ECG findings, aspirin 324 mg (chewed and swallowed), clopidogrel 600 mg, and morphine 4 mg intravenously once were administered before transfer. Notes also show that β-blockers and nitroglycerin were held because of bradycardia and hypotension.

His past medical history is significant for nonadherence, hypertension, diabetes, dyslipidemia, and heart failure with preserved ejection fraction (HF*p*EF), with a last-reported left ventricular ejection fraction (LVEF) of 65% 1 year ago. The patient reports that he currently takes no medications at home.

- Vital signs on transfer: blood pressure 87/52 mm Hg, heart rate 110 beats/minute, respiratory rate 19 breaths/minute, temperature 99.7°F (37.6°C)
- The team's physical assessment indicates ongoing distress, radiating chest pain 7/10, evidence of rales, absence of any cardiac murmurs, and presence of a right radial arterial line.
- A preexisting urinary catheter with 20 mL of urine in the reservoir is also present (the patient reports that his most recent void was yesterday morning).

According to outlying hospital records, only 30 mL of urine was reported before time of transfer.

- His chest radiography reveals evidence of diffuse patchy opacities; however, the report indicates that an infiltrate cannot be ruled out.
- His serum chemistry panel results are as follows: sodium 132 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 34 mg/dL, serum creatinine (SCr) 1.9 mg/dL, and glucose 163 mg/dL.
- Results of the complete blood cell count (CBC) are as follows: white blood cell count (WBC) 11.3 × 10^3 cells/mm^3, hemoglobin 10.9 g/dL, hematocrit 31.1%, and platelet count 213,000/mm^3.
- Additional laboratory values include troponin-T 3.9 ng/mL, aspartate aminotransferase (AST) 14 IU/L, alanine aminotransferase (ALT) 46 IU/L, hemoglobin A1C (A1C) 8.3%, and brain natriuretic peptide (BNP) of 1423 pg/mL.

1. Which is the most likely cause of this patient's admission and transfer?
   A. Septic shock caused by suspected pneumonia with subsequent myocardial depression and demand ischemia.
   B. Cardiogenic shock caused by acute on chronic decompensated systolic heart failure (HF).
   C. Cardiogenic shock caused by a suspected inferior ST-segment elevation myocardial infarction (STEMI).
   D. Cardiogenic shock caused by a suspected non–ST-segment elevation myocardial infarction (NSTEMI) affecting the lateral wall.

2. Given this patient's presentation, which coronary artery is most likely to be the culprit lesion?
   A. Left main coronary artery.
   B. Left anterior descending artery.
   C. Left circumflex coronary artery.
   D. Right coronary artery.

3. The interventional cardiologist who is evaluating the patient for potential revascularization asks the ICU team to place a central venous catheter. Which changes/interventions regarding this patient's hemodynamic support would be best to recommend?
   A. Increase dopamine to achieve a mean arterial pressure (MAP) greater than 65 mm Hg.
   B. Convert the patient to norepinephrine, and titrate the dose to achieve a MAP greater than 65 mm Hg while weaning off dopamine.
   C. Initiate milrinone at 0.375 mcg/kg/minute, and continue dopamine at 15 mcg/kg/minute.
   D. Administer 1000 mL of normal saline as a bolus because of low urine output.

4. The patient has been taken to the cardiac catheterization laboratory, and a "code blue" is called overhead for immediate emergency response to this patient's procedural area. On arrival, chest compressions have just been paused for defibrillation, and a single dose of epinephrine has been administered. The interventional team indicates that, when attempting visualization of the right coronary artery, the patient went into ventricular tachycardia (VT). The patient's telemetry monitor now shows sinus tachycardia with noted ectopy—heart rate 113 beats/minute and blood pressure 84/52 mm Hg. The cardiologist asks for recommendations for an antiarrhythmic because he is concerned about a VT recurrence, given the bigeminy on telemetry. Which agent would be best to recommend?
   A. Lidocaine 100 mg intravenous push for 2–3 minutes, followed by an infusion at 1 mg/minute.
   B. Amiodarone 300 mg intravenous push for less than 1 minute.
   C. Metoprolol 10 mg intravenous push for 1–2 minutes.
   D. Diltiazem 20 mg intravenous push for 2 minutes, followed by a continuous infusion at 5 mg/hour and titrated to maintain a heart rate less than 110 beats/minute.

5. The patient returns to the ICU after his left heart catheterization, which was performed through the femoral artery. In addition to his acute decompensation, which major procedural complication is of greatest concern during the next 12 hours?
   A. Bleeding (particularly retroperitoneal bleeding).
   B. Dissection/rupture.
   C. Stent thrombosis.
   D. Papillary muscle rupture.

6. The patient returns to the ICU with a pulmonary artery catheter in place and is currently receiving dopamine at 12 mcg/kg/minute and norepinephrine at 0.08 mcg/kg/minute with heart rate 108 beats/minute, blood pressure 82/51 mm Hg, cardiac index 2.0, central venous pressure (CVP) 26 mm Hg, and pulmonary artery pressure 49/21 mm Hg. The physician is concerned about right ventricular dysfunction in the setting of shock and approaches you for a recommendation to increase blood pressure (BP). Ideally, the physician would prefer to wean dopamine and minimize further increases in pulmonary vascular resistance (PVR) because of the presence of pulmonary hypertension. Which strategy would be best to recommend?

   A. Keep the current infusions, and reevaluate later.
   B. Initiate phenylephrine at 1 mcg/kg/minute, and wean the dopamine off if MAP is greater than 65 mm Hg.
   C. Initiate vasopressin at 0.04 unit/minute, and wean the dopamine off if MAP is greater than 65 mm Hg.
   D. Administer a 1-L bolus of normal saline, and wean the dopamine off if MAP is greater than 65 mm Hg.

7. Hours later, this patient goes into atrial fibrillation (AF) with a heart rate of 126 beats/minute; however, the patient's blood pressure remains 86/56 mm Hg according to the regimen selected in the previous question. Which agent would you most likely administer to manage the patient's AF?

   A. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute.
   B. Amiodarone 150 mg intravenous infusion for 10 minutes, followed by a continuous infusion at 1 mg/minute.
   C. Metoprolol 5 mg intravenous push once, followed by 5 mg intravenous push every 6 hours.
   D. Diltiazem 20 mg intravenous push, followed by a continuous infusion at 5 mg/hour and titrated to maintain a heart rate of less than 110 beats/minute.

8. Which medication-related quality metric would not require documentation of contraindications based on this patient's clinical presentation (acute MI with preserved LVEF)?

   A. Aspirin contraindication.
   B. Statin contraindication.
   C. β-Blocker contraindication.
   D. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) contraindication.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

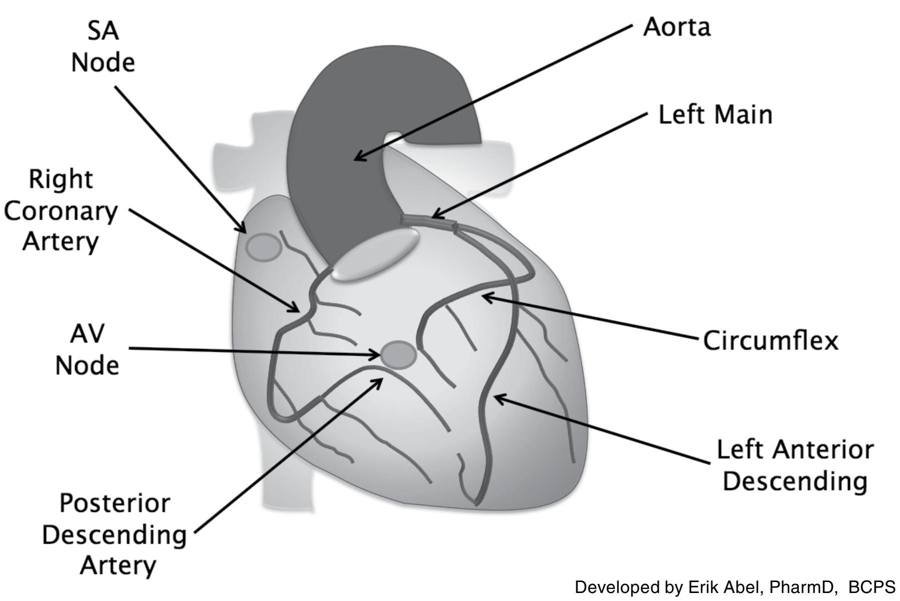
1. Domain 1: Critical Care
    a. Task A: 1, 2
    b. Task B: 1
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 2
    b. Task B: 2
    c. Task C: 2, 3
3. Domain 3: Professional Practice
    a. Task B: 1

I. CARDIOVASCULAR FUNDAMENTALS OVERVIEW

A. Cardiac output is defined as:
  1. Heart rate × stroke volume
    a. Stroke volume is influenced by:
      i. Preload: Volume of blood (represented in most cases by a pressure) in a ventricular cavity at the end of diastole imparting stretch on a resting myocardial sarcomere
      ii. Afterload: The pressure that a ventricle must overcome to generate cardiac output. The greater the afterload (vascular resistance or impedance), the greater the amount of energy and force required to enable ejection of blood from a ventricle.
      iii. Contractility: Refers to the intrinsic ability of cardiac muscle fibers to contract and generate force independently of changes in muscle fiber length or preload. It is a measure of the heart's strength and efficiency in pumping blood and is influenced by factors like calcium availability, sympathetic stimulation, and certain medications.

B. The myocardium has 5 functions and distinctive properties:
  1. Chronotropy refers to the effect on the pulse rate, with positive chronotropy increasing it and negative chronotropy decreasing it.
  2. Dromotropy refers to the influence on the speed of electrical conduction through the heart, particularly through the atrioventricular (AV) node.
  3. Inotropy refers to the effect on the strength or force of myocardial contraction, with positive inotropy increasing and negative inotropy decreasing contractility.
  4. Bathmotropy refers to the effect on the heart's excitability, or its ability to respond to stimuli, with positive bathmotropy increasing and negative bathmotropy decreasing this sensitivity.
  5. Lusitropy refers to the effect on the heart's relaxation during diastole, with positive lusitropy enhancing relaxation and negative lusitropy impairing it.

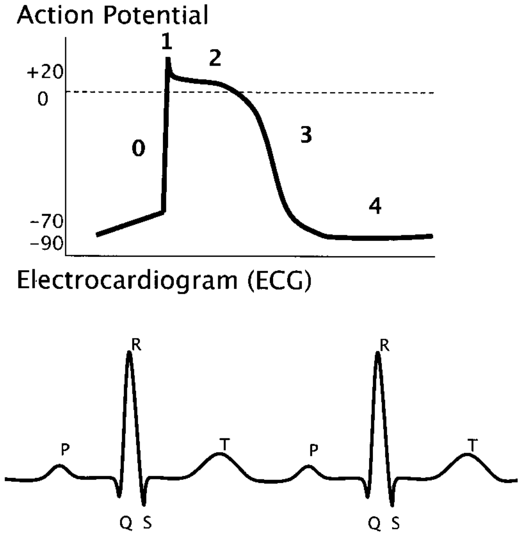
C. Coronary Artery Circulation
  1. Myocardial perfusion in the coronary arteries that bifurcate off the left main occurs during diastole, whereas the right coronary artery fills during both systole and diastole, making it highly dependent on systolic blood pressure to maintain coronary perfusion.
  2. Coronary artery anatomy and perfusion are not the same in everyone.
  3. ECG abnormalities, hemodynamic assessment, and patient symptoms may assist with coronary artery disease (CAD) localization.
  4. Circulatory dominance:
    a. Right dominant: Posterior descending artery and AV nodal artery arise from the right coronary artery (85% of the population).
    b. Left dominant: Posterior descending artery arises from the circumflex artery (8% of the population).
    c. Codominant: Posterior descending artery arises from branches of the circumflex and the right coronary artery (7% of the population).
    d. Other notable variations: The sinoatrial (SA) node may have variation in the vessels that supply it; it is most commonly perfused by the right coronary artery (about 70%), circumflex (about 25%), or right coronary artery and circumflex (about 5%).


SA Node
Aorta
Left Main
Right Coronary Artery
Circumflex
AV Node
Left Anterior Descending
Posterior Descending Artery

Developed by Erik Abel, PharmD, BCPS

Figure 1. Coronary artery circulation.

D. Cardiac Anatomy in Relation to the ECG (Figure 2)
   1. A single lead of an ECG tracing is a summative representation of the action potentials occurring from a single cell, facilitating myocardial conduction, contraction, and relaxation.
   2. A 12-lead ECG can provide a geographic representation of conduction within the myocardial tissue. Conduction abnormalities within specified leads may indicate perfusion defects in some clinical scenarios (i.e., acute coronary syndromes [ACS]).



Phase	Electrolyte movement	Conduction change
0	Na^+ influx into cell	Depolarization
1	K^+ and Cl^- out of cell	Repolarization
2	Ca^{2+} into cell and K^+ out of cell	Plateau
3	K+ out of cell	Repolarization
4	Resting Membrane Potential	

ECG point	Representation
P	Sinoatrial (SA) node impulse generation/atrial depolarization
PR interval	Duration for conduction to occur from the SA node through the AV node, bundle of His, bundle branches and Purkinje fibers
QRS	Concurrent atrial repolarization and ventricular depolarization
ST segment	Ventricular refractory period
T	Ventricular repolarization
QT interval	Duration for ventricular repolarization
RR interval	Duration between ventricular depolarizations (represents heart rate)
U	Further ventricular depolarizations not listed or commonly visualized; may be more prominent in hypothermia, bradycardia, or severe electrolyte depletions

12 — Lead Electrocardiogram (ECG)

Limb leads				Precordial Leads			
I	Anterolateral (Circumflex)	aVR		V1	Anteroseptal (LAD)	V_4	Anteroapical (Distal LAD)
II	Inferior (RCA)	aVL	Anterolateral (Circumflex)	V2	Anteroseptal (LAD) Posterior (RCA)	V_5	Anterolateral (Circumflex)
III	Inferior (RCA)	aVF	Inferior (RCA)	V3	Anteroapical (Distal LAD) Posterior (RCA)	V_6	Anterolateral (Circumflex)

adapted from ACLS instructor book

Figure 2. Cardiac Anatomy in relation to the ECG.

II. HEMODYNAMIC MANAGEMENT AND THE HEART

A. Hemodynamic Assessment Relies on the Clinician's Ability to:
   1. Understand cardiovascular circulation (Figure 3) and pathophysiology contributing to the hemodynamic variables in isolation and in the context of other changes and conditions.
   2. Account for hemodynamic trends in view of end-organ function and use surrogates of oxygen delivery.
   3. Understand the roles of hemodynamic tools, limitations of use, and interpretation of the devices/technology.
   4. Identify appropriate therapeutic targets (Figure 4), and apply the pharmacologic/pharmacodynamic principles (Table 1) to initiate, modify, or discontinue therapy depending on clinical response.

B. Advantages and Disadvantages of Invasive Hemodynamic Monitoring for Assessing Cardiac Output and/or Volume Status
   1. Hemodynamic monitoring techniques facilitate diagnosis
   2. Therapy guided by clinical assessment and a pulmonary artery catheter compared with clinical assessment alone for HF did not result in differences in overall mortality or hospitalizations. However, more anticipated adverse events (i.e., infection, bleeding) were seen with pulmonary artery catheter-guided care (JAMA 2005;294:1625-33).

3. However, for patients with SCAI Stages C–E cardiogenic shock, using pulmonary artery catheter-derived hemodynamic data has been associated with improved mortality (J Am Coll Cardiol HF 2020;8:903-13).
4. A recent prospective trial showed that providers, regardless of training level (intern to advanced HF attending), do not accurately identify cardiogenic shock on physical examination alone. The positive and negative predictive values of clinical assessment compared with right heart catheterization in cardiogenic shock were 74.7% and 50.4% (*J Card Fail*. 2020;26(2):128-135).
5. Diligent use and skilled interpretation of these technologies, together with patient assessment, can be used to guide therapeutic interventions.
6. See comparisons of invasive and minimally invasive hemodynamic monitoring devices (Table 2 in the Shock Syndromes I chapter).

C. Pharmacologic Support in Cardiovascular Critical Illness (see Table 1)

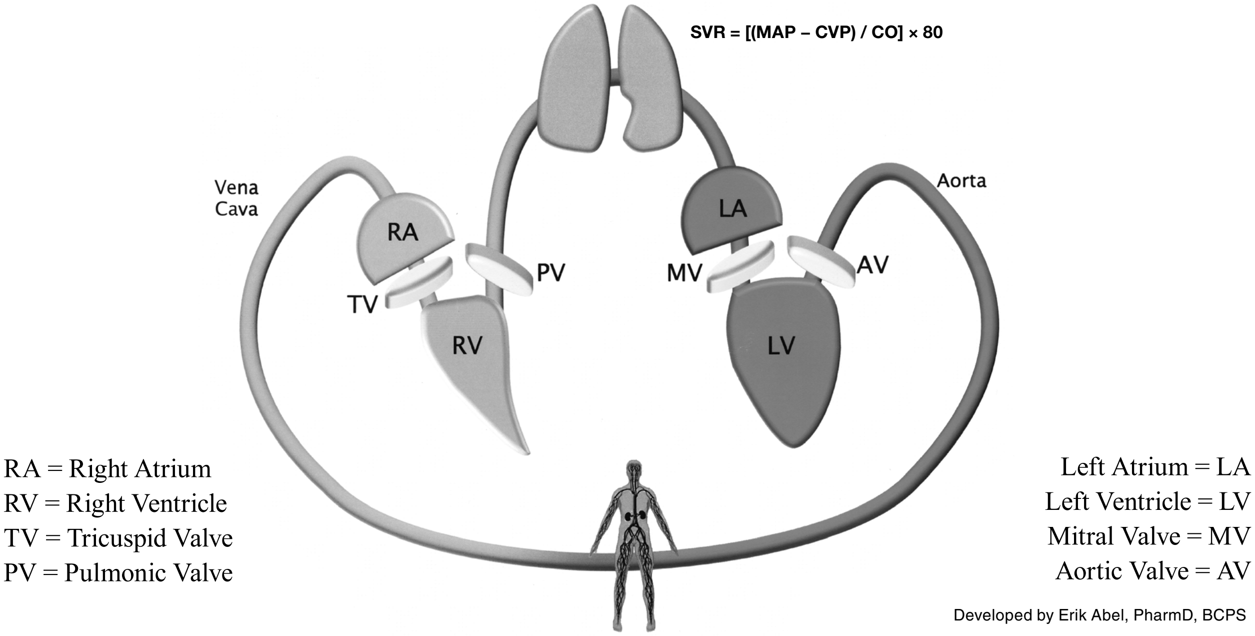

SVR = [(MAP – CVP) / CO] × 80
Vena Cava
Aorta
RA
LA
PV
MV
AV
TV
RV
LV
RA = Right Atrium
RV = Right Ventricle
TV = Tricuspid Valve
PV = Pulmonic Valve
Left Atrium = LA
Left Ventricle = LV
Mitral Valve = MV
Aortic Valve = AV

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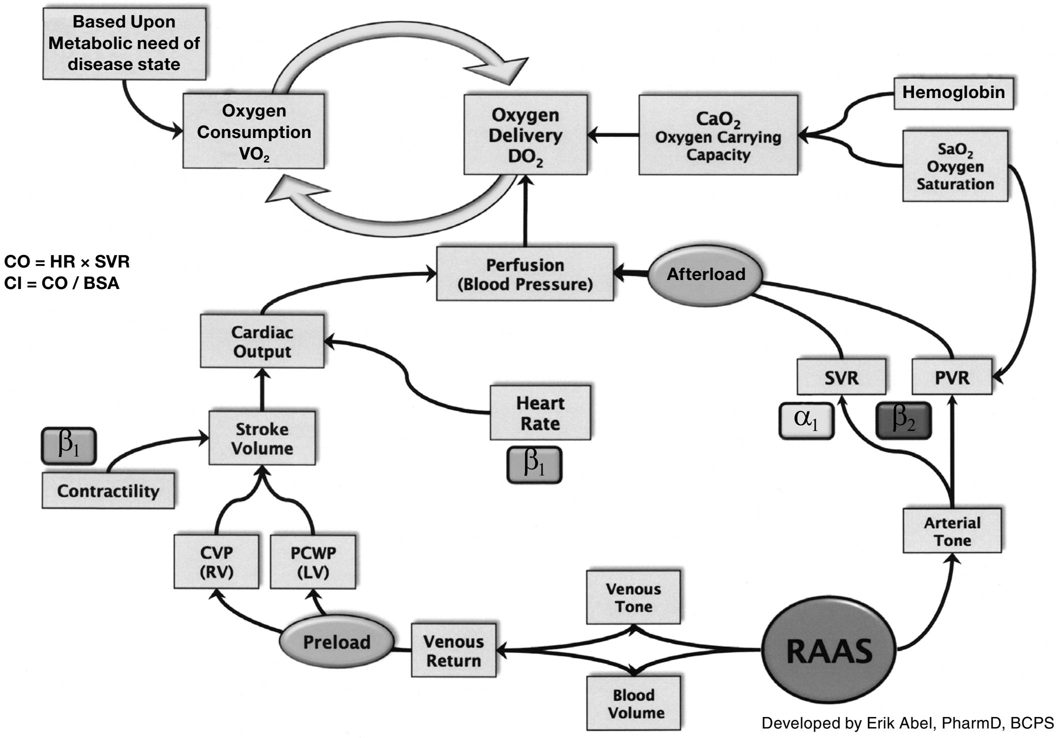
Figure 3. Cardiovascular systemic circulation.


Based Upon Metabolic need of disease state
Oxygen Consumption VO₂
Oxygen Delivery DO₂
CaO₂ Oxygen Carrying Capacity
Hemoglobin
SaO₂ Oxygen Saturation
CO = HR × SVR
CI = CO / BSA
Perfusion (Blood Pressure)
Afterload
Cardiac Output
Heart Rate
β1
SVR
PVR
α1
β2
β1
Stroke Volume
Contractility
Arterial Tone
CVP (RV)
PCWP (LV)
Venous Tone
Preload
Venous Return
RAAS
Blood Volume

Developed by Erik Abel, PharmD, BCPS

Figure 4. Integrated model of the hemodynamic variables and therapeutic targets.

BSA = body surface area; CI = cardiac index; CO = cardiac output; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance.

Table 1. Pharmacologic Support in Cardiovascular Critical Illness

Vasopressors	Dopa	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Dopamine[a]	+++++	+++	++++	++		↑	↔	↑	↔ or ↑	↔ or ↑
Epinephrine		++++	++++	+++		↑	↔ or ↑	↑	↑	↑
Norepinephrine		+++++	+++	++		↑ or ↔	↑	↑ or ↔	↑	↑
Phenylephrine		+++++				↔ or ↓	↑	↔ or ↓	↑	↑
Vasopressin	N/A “α_1-like effects”				V_1 and V_2 agonism	↔ or ↓	↑	↔ or ↓	↑	↔ or ↓
Angiotensin II	N/A “α_1-like effects”				AT1 receptor agonism	↔ or ↓	↑	↔ or ↓	↑	↔ or ↑
Inotropes										
Dobutamine		+	++++	++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔ or ↓	↑	↔ or ↓	↔ or ↓
Milrinone[b]	N/A “B_1 and β_2-like effects”				PDE_3 inhibition	↑	↓	↑	↓	↓

Table 1. Pharmacologic Support in Cardiovascular Critical Illness *(continued)*

Vasoactives	Dopa	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Vasodilators										
Nitroglycerin					cGMP	↔ or ↑	↓	↔ or ↑	↔ or ↓	↔ or ↓
Nitroprusside					cGMP	↔ or ↑	↓	↔ or ↑	↓	↓
Nitric oxide (inhaled)					cGMP	N/A	↔	↔ or ↑	↔	↓
Epoprostenol (inhaled)					cAMP	N/A	↔	↔ or ↑	↔	↓

[a] High doses associated with increasing α_1 activity.

[b] Normal half-life is 2.5 hours, but drug is eliminated renally. Loading dose rarely used in routine management because of hypotension.

AMP = cyclic adenosine monophosphate; AT1 = angiotensin II type 1; cGMP = cyclic guanosine monophosphate; CVP = central venous pressure; HR = heart rate; N/A = not applicable; PDE3 = phosphodiesterase type 3; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance. Information from: Br J Pharmacol 2012;165:2015-33; J Am Coll Cardiol 2014;63:2069-78; Pathophysiol Heart Dis 2011:xiv; Circulation 2008;118:1047-56; Crit Care Med 2014:xix; J Pharm Pract 2011;24:44-60.

III. CARDIOGENIC SHOCK

A. Characterized by three hallmarks:
   1. Sustained hypotension unresponsive to fluid administration alone (systolic blood pressure [SBP] less than 90 mm Hg for at least 30 minutes) (Cardiol Clin 2013;4:567-80)
   2. Evidence of myocardial dysfunction with reduced cardiac index (less than 2.2 L/minute/m^2)
   3. Signs and symptoms of malperfusion in the setting of volume overload and elevated cardiac filling pressures (e.g., pulmonary capillary wedge pressure greater than 18 mm Hg)

B. Society for Cardiovascular Angiography and Interventions (SCAI) Classifications for Cardiogenic Shock (Catheter Cardiovasc Interv 2019;94:29-37):
   1. Stage A – at risk. These patients are not in shock but are at risk of future development.
   2. Stage B – beginning. These patients have clinical evidence of relative hypotension or tachycardia without hypoperfusion.
   3. Stage C – classic. These patients have evidence of hypotension and hypoperfusion requiring intervention, including vasoactive therapies and mechanical circulatory support.
   4. Stage D – deteriorating. These patients are those in stage C who are getting worse despite attempts to restore optimal hemodynamics.
   5. Stage E – extremis. These patients are experiencing cardiac arrest with ongoing cardiopulmonary resuscitation or extracorporeal membrane oxygenation (ECMO).

C. Signs and Symptoms: See Heart Failure section.

D. Epidemiology: Without appropriate diagnosis and management, in-hospital mortality rates as high as 60% have been described (Semin Respir Crit Care Med 2011;32:598-606).

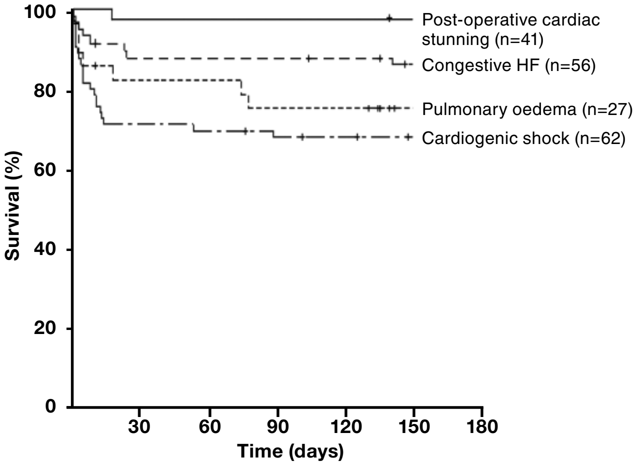


Figure 5. Survival rates of ICU patients over time presenting with different acute heart failure syndromes (Crit Care 2010;14:201).

E. Etiology
  1. Usually caused by left ventricular (LV) failure secondary to an acute MI, but a list of other potential causes can be found in Box 1
  2. May be multifactorial, including one or more of the causative etiologies; however, can also coexist with other types of shock syndromes

Box 1. Potential Causes of Cardiogenic Shock (Critical Care Medicine 2014:xix; Cardiol Clin 2013;31:567-80, viii; Cardiol Clin 2013;31:519-31, vii-viii; Semin Respir Crit Care Med 2011;32:598-606)

LV Failure
- Large MI
- Small MI with preexisting systolic HF
- Reinfarction
- Septic shock with severe myocardial depression

RV Failure
- RV infarction
- End-stage pulmonary hypertension

Acute Mechanical Dysfunction
- Papillary muscle rupture or chordal rupture with subsequent severe mitral regurgitation
- Free-wall rupture
- Ventricular septal rupture
- Cardiac tamponade

Cardiomyopathy
- End-stage HF
- Myocarditis
- Peripartum cardiomyopathy
- Left ventricular outflow tract obstruction
- Stress-induced cardiomyopathy (i.e., Takotsubo)

Valvular Disease
- Acute aortic regurgitation
- Ischemic mitral regurgitation
- Aortic or mitral stenosis with tachyarrhythmia or other condition causing decompensation
- Infectious endocarditis
- Prosthetic valve dysfunction or thrombosis

Arrhythmias
- Atrial tachyarrhythmias
- Ventricular tachyarrhythmias
- Bradycardia

Other Conditions
- Prolonged cardiopulmonary bypass and/or coronary air embolus
- Cardiac trauma (blunt or penetrating)
- Heart transplant rejection
- Pulmonary embolism
- Medical nonadherence

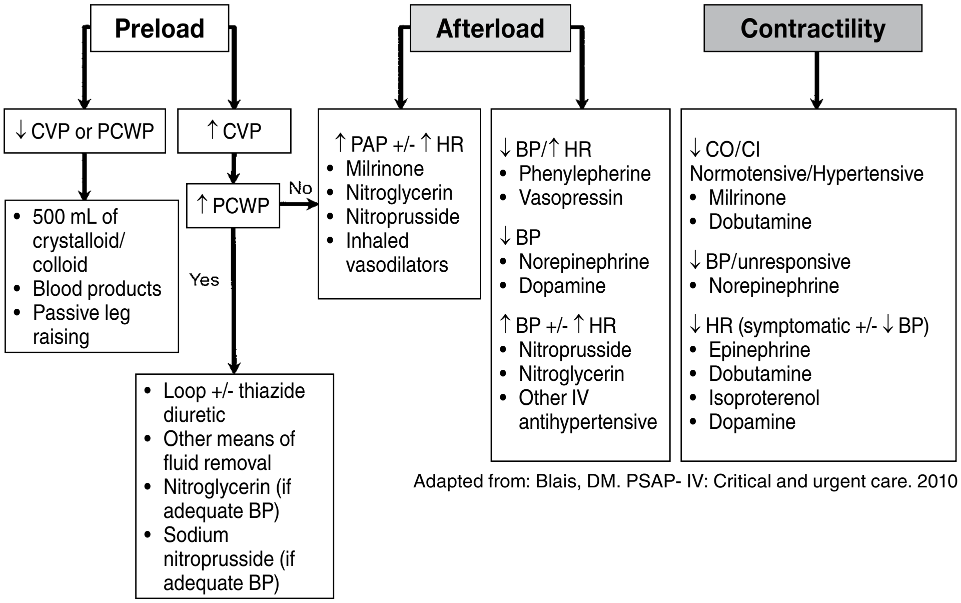
HF = heart failure; LV = left ventricular; MI = myocardial infarction; RV = right ventricular.

F. Resuscitation/Treatment
   1. Treatment largely depends on managing underlying chronic or acute cardiovascular disease(s) outlined in Box 1, with consideration given to chronicity of clinical changes before onset of shock.
   2. Means of management will be primarily discussed under the Major Contributing Etiologies headings in sections IV–VII.
   3. Hemodynamic management and pharmacotherapeutic considerations
      a. Because cardiogenic shock may have different underlying, contributing etiologies, hemodynamic management requires careful interpretation of clinical values. Treatment strategies could be devised according to the algorithm in Figure 6.

b. Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock (DOREMI) (N Engl J Med 2021;385:516-25)
    i. First prospective trial studying milrinone and dobutamine for cardiogenic shock management (n=192) during the index hospitalization
        (a) Median ejection fraction was 25%, and around two-thirds of patients had ischemic cardiomyopathy. Most patients (90%) fell into SCAI cardiogenic shock classes C (classic) and D (deteriorating).
        (b) Milrinone or dobutamine was initiated at a dose determined by a standard dosing scale ranging from 1 to 5, corresponding to 2.5, 5, 7.5, 10, and greater than 10 mcg/kg/minute for dobutamine and 0.125, 0.25, 0.5, and greater than 0.5 mcg/kg/minute for milrinone. Inotropes were adjusted in a blinded fashion.
    ii. Composite primary outcome (in-hospital mortality from any cause, resuscitated cardiac arrest, receipt of cardiac transplantation, or mechanical circulatory support, nonfatal MI, transient ischemic attack or stroke, or initiation of renal replacement therapy) did not differ between the two groups. Of importance, this study highlights the persisting high mortality rates in patients with cardiogenic shock (around 40%).
    iii. Both dobutamine and milrinone had high rates of arrhythmias leading to intervention, and there was no difference in sustained hypotension or vasopressor requirements for either medication.

c. Sepsis Occurrence in Acutely Ill Patients (SOAP) II landmark trial (N Engl J Med 2010;362:779-89)
    i. International multicenter trial (n=1679) that compared the 28-day mortality of norepinephrine with that of dopamine in the management of shock
        (a) Included if signs of malperfusion and MAP less than 70 mm Hg or SBP less than 100 mm Hg, despite adequate fluid challenge (at least 1000 mL of crystalloids or 500 mL of colloids unless the CVP was greater than 12 mm Hg or the pulmonary artery occlusion pressure was greater than 14 mm Hg)
        (b) Allowed titration to maximums of norepinephrine 0.19 mcg/kg/minute versus dopamine 20 mcg/kg/minute, after which open-label norepinephrine was allowed (open-label norepinephrine doses did not exceed 1.1 mcg/kg/minute during the study period)
        (c) Epinephrine and vasopressin were permitted as rescue agents (similar use in both groups).
        (d) Dobutamine use was greater in the norepinephrine group (19.4% vs. 14.8%).
    ii. Showed that dopamine was associated with a significantly higher mortality rate than was norepinephrine with or without dobutamine in patients with cardiogenic shock in subgroup analysis
    iii. Dopamine was associated with more adverse events than norepinephrine in the management of all shock subtypes, predominantly driven by the incidence of arrhythmias (24.1% vs. 12.1%, $p<0.001$). Tachyarrhythmias with dopamine had the greatest incidence within the first 36 hours after randomization.

d. Study Comparing the Efficacy and Tolerability of Epinephrine and Norepinephrine in cardiogenic shock [OptimaCC] (J Am Coll Cardiol 2018;72:173-82)
    i. Prospective, double-blind, multicenter, randomized study (n=57) that compared cardiac index evolution and refractory cardiogenic shock between epinephrine and norepinephrine in patients with cardiogenic shock post-MI
    ii. Trial showed that cardiac index evolution did not differ between groups, though the rate of refractory cardiogenic shock was significantly higher in the epinephrine arm than in the norepinephrine arm (37% vs 7%). However, this was largely driven by an increase in lactic acid in the epinephrine group. Epinephrine is a known cause of type B lactic acidosis.
    iii. Tachycardia and lactic acidosis were also significantly increased in the epinephrine group.


Preload
Afterload
Contractility
↓ CVP or PCWP
↑ CVP
• 500 mL of crystalloid/ colloid
• Blood products
• Passive leg raising
↑ PCWP
No
Yes
• Loop +/- thiazide diuretic
• Other means of fluid removal
• Nitroglycerin (if adequate BP)
• Sodium nitroprusside (if adequate BP)
↑ PAP +/- ↑ HR
• Milrinone
• Nitroglycerin
• Nitroprusside
• Inhaled vasodilators
↓ BP/↑ HR
• Phenylepherine
• Vasopressin
↓ BP
• Norepinephrine
• Dopamine
↑ BP +/- ↑ HR
• Nitroprusside
• Nitroglycerin
• Other IV antihypertensive
↓ CO/CI
Normotensive/Hypertensive
• Milrinone
• Dobutamine
↓ BP/unresponsive
• Norepinephrine
↓ HR (symptomatic +/- ↓ BP)
• Epinephrine
• Dobutamine
• Isoproterenol
• Dopamine

Adapted from: Blais, DM. PSAP- IV: Critical and urgent care. 2010

Figure 6. Shock management and treatment considerations based on hemodynamic indices.

Patient Case

Questions 1–8 pertain to the following case.
J.M. is a 68-year-old man with a history of CAD including STEMI 6 months ago with placement of two drug-eluting stents, type 2 diabetes, hypertension, dyslipidemia, gastroesophageal reflux disease, obstructive sleep apnea, frequent epistaxis, ischemic cardiomyopathy (LVEF 30%–35%), and moderate to severe mitral regurgitation. He is admitted to the cardiac intensive care unit for severe shortness of breath and altered mental status, and he is currently on continuous positive airway pressure (CPAP). He has gained 13 kg during the past 2 weeks (now weighs 121 kg) and has had decreased urine output, despite having had his diuretic dose increased. Home medications include the following: aspirin 81 mg once daily, ticagrelor 90 mg every 12 hours, pantoprazole 40 mg once daily, atorvastatin 40 mg once daily, insulin glargine 10 units every night, metformin 500 mg every 12 hours, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. His wife states that he was taking clopidogrel until 1 month ago, at which time he was given ticagrelor samples from his primary care physician because of cost concerns. A physical examination reveals rales throughout his lung fields. He is afebrile, anxious, and alert.

1. Given J.M.'s comorbidities, some drugs or drug classes have proven mortality benefits. Which medications could be added or modified to the patient's home medication profile to further slow disease progression and improve mortality?
   A. Amlodipine, clopidogrel, and sitagliptin
   B. Spironolactone, lisinopril, and carvedilol
   C. Pravastatin, amlodipine, and aspirin
   D. Prasugrel, sildenafil, and atenolol

Patient Case *(contined)*

2. Given the patient's presentation, which group of diagnostic tests would be most helpful to guide your recommendations to the team for J.M.'s current management? (Assume that a basic metabolic panel [Chem 7], a pulse oximetry, and a capillary blood glucose have already been completed.)
    A. Urine culture, respiratory culture, lactate, and procalcitonin
    B. Chest radiography, arterial blood gas (ABG), liver function tests, and serial troponins
    C. Chest radiography, echocardiogram (ECHO), lactate, and BNP
    D. Chest radiography, arterial line, ABG, and lactate

3. All tests previously mentioned have been ordered, and the following results are available. J.M.'s blood pressure is 90/56 mm Hg (MAP 67 mm Hg), and his heart rate is 56 beats/minute. A 12-lead ECG showed normal sinus rhythm without evidence of acute ST-T changes.
    - Chest radiography reveals diffuse patchy opacities; however, infiltrate cannot be ruled out; lines are all in appropriate positions.
    - Serum chemistry panel results are as follows: sodium 126 mEq/L, potassium 4.8 mEq/L, chloride 102 mEq/L, carbon dioxide 21 mEq/L, BUN 32 mg/dL, SCr 1.6 mg/dL, and glucose 134 mg/dL.
    - Results of the CBC are as follows: WBC 9.8×10^3 cells/mm^3, hemoglobin 11.1 g/dL, hematocrit 32.6%, and platelet count 173,000/mm^3.
    - Additional laboratory values include the following: troponin 0.9 ng/mL, AST 114 IU/L, ALT 102 IU/L, and BNP 1936 pg/mL.
    - Invasive hemodynamic variables include CVP 28 mm Hg, pulmonary artery pressures 46/22 mm Hg, cardiac index 1.8 L/minute/m^2, and $Scvo_2$ 53%; pulmonary artery occlusion pressure is not yet available.
    - ABG results are as follows: pH 7.36, partial pressure of oxygen (Po_2) 93.7, partial pressure of carbon dioxide (Pco_2) 43.2, bicarbonate 23.9, oxygen (O_2) saturation 89%, and lactate 6.9.
    - ECHO results are pending.

    The patient's physical examination reveals that his extremities are cold to the touch, and his capillary refill is poor. The team has ordered furosemide 80 mg intravenously once and would like to initiate a vasopressor or inotrope for this patient. Which would be best to recommend at this time?

    A. Norepinephrine 0.08 mcg/kg/minute
    B. Epinephrine 0.08 mcg/kg/minute
    C. Milrinone 0.75 mcg/kg/minute
    D. Dobutamine 5 mcg/kg/minute

IV. ACUTE CORONARY SYNDROMES

A. Pathophysiology
    1. Manifestation of prolonged cessation of oxygenated blood supply to a portion of the myocardium that is most commonly caused by an acute thrombus at the site of coronary atherosclerotic plaque rupture leading to local or regional myocardial ischemia and necrosis
    2. Other disease states leading to an elevated myocardial oxygen demand with a concurrent inability to meet such demands may result in a scenario where "demand ischemia (type II NSTEMI)" is considered versus a diagnosis of ACS.

B. Presentation and Diagnosis (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425) – Although other cardiac enzymes assays are available for clinical use, cardiac troponins are usually used as sensitive markers indicative of myocardial necrosis, with a negative troponin conferring a greater than 95% negative predictive value for MI. Troponin is eliminated renally, so patients with end-stage renal disease often have elevations in cardiac troponin without other evidence of myocardial ischemia. Therefore, other clinical signs and symptoms of acute coronary syndromes as well as the rate of troponin increase should be assessed.

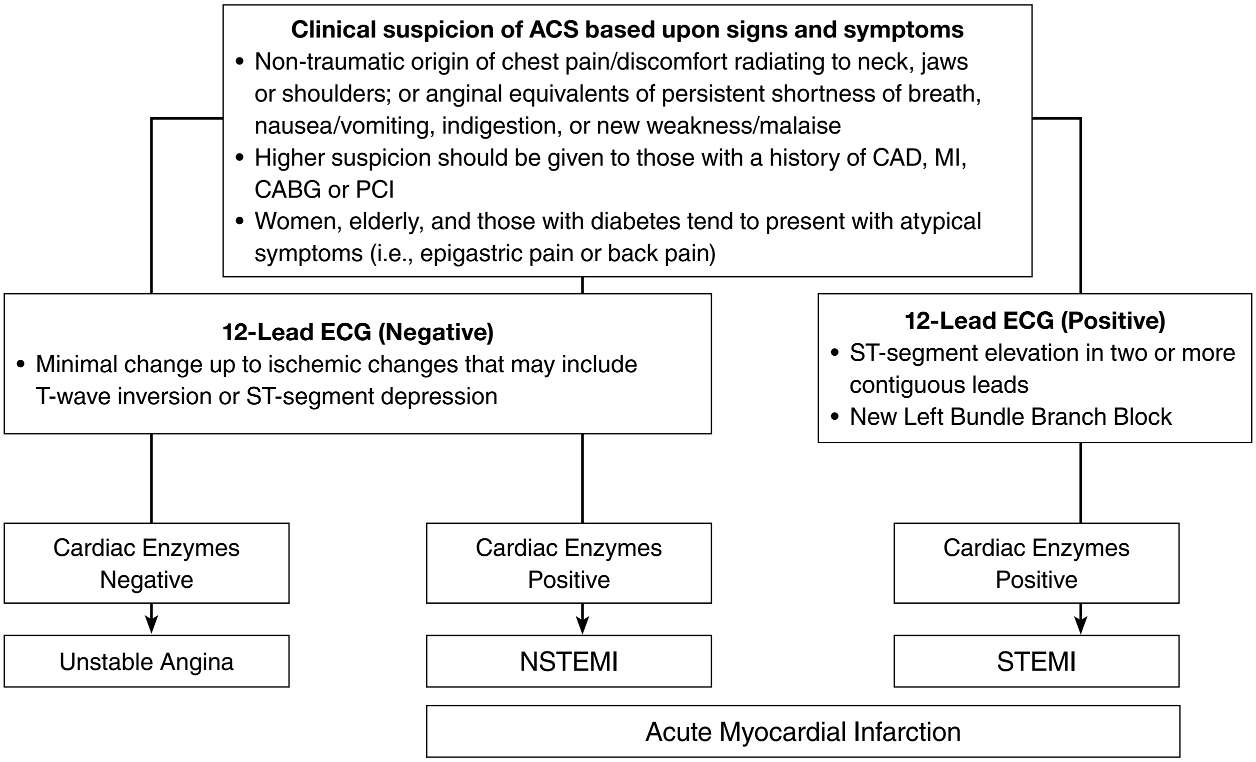

Clinical suspicion of ACS based upon signs and symptoms
• Non-traumatic origin of chest pain/discomfort radiating to neck, jaws or shoulders; or anginal equivalents of persistent shortness of breath, nausea/vomiting, indigestion, or new weakness/malaise
• Higher suspicion should be given to those with a history of CAD, MI, CABG or PCI
• Women, elderly, and those with diabetes tend to present with atypical symptoms (i.e., epigastric pain or back pain)
12-Lead ECG (Negative)
• Minimal change up to ischemic changes that may include T-wave inversion or ST-segment depression
12-Lead ECG (Positive)
• ST-segment elevation in two or more contiguous leads
• New Left Bundle Branch Block
Cardiac Enzymes Negative
Cardiac Enzymes Positive
Cardiac Enzymes Positive
Unstable Angina
NSTEMI
STEMI
Acute Myocardial Infarction

Figure 7. Acute coronary syndrome (ACS) presentation and diagnosis.

Box 2. Causes of Troponin Elevation (Heart 2006;92:987-93)

Acute decompensated heart failure	Early post-cardiac surgery
Acute MI	Heart transplantation
Acute pulmonary embolism	Myocarditis
Aortic stenosis	Pericarditis
Cardiac amyloidosis	Post-PCI
Cardiotoxic chemotherapy	Rhabdomyolysis
Chest compressions	Sepsis
Chest wall trauma or compressions	Severe strenuous exercise
Chronic heart failure	Tachyarrhythmia
Direct current cardioversion/defibrillation	Type A aortic dissection

PCI = percutaneous coronary intervention.

C. Acute Management of MI

Table 2. Acute Management (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425)

	STEMI	NSTEMI/ Unstable Angina
Goals of care	Reperfusion therapy as soon as possible • Primary PCI preferred if it can be performed within 90 min of first medical contact • If primary PCI is not immediately available, and the delay from hospital presentation to PCI is anticipated to be >120 min; fibrinolytic should be administered within 30 min of presentation unless contraindications exist • Surgical revascularization may be indicated, depending on severity of CAD, complexity of anatomy, or development of other complications	Prevent total occlusion of the vessel • Decision and need for revascularization (PCI or surgery) vs. medical management should be made on the basis of risk stratification, symptom resolution, and indicators of ongoing myocardial damage/ischemia

CAD = coronary artery disease.

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425)

Predominant interventions on presentation/onset for stabilization – Any ACS	
Morphine or other narcotic analgesic	• Theoretical benefit of morphine was to treat pain and reduce myocardial and microvascular damage by inducing vasodilation and mediate some degree of preload reduction, thereby decreasing myocardial oxygen demand. However, morphine use has largely fallen out of favor, and morphine should only be used for severe refractory chest pain despite nitroglycerin • Morphine is also an independent predictor of high residual platelet reactivity in ticagrelor/prasugrel use (may impair absorption because of delayed gastric emptying) (Am Heart J 2014;6:909-14) • Morphine now carries a class IIb-B recommendation given that at least two large trials have identified an association between morphine administration and risk of death (N Engl J Med 2014;371:1016-27; Am Heart J 2005;149:1043-9; J Am Coll Cardio. 2014;64:e139-228) • Studies evaluating fentanyl in the population with ACS have also shown high residual platelet reactivity. Given this risk, opioids should be avoided (*Circulation*. 2018;137(3):307-309)
Oxygen	• Can help attenuate anginal pain secondary to tissue hypoxia • Current evidence shows no benefit for supplemental oxygen (and potential harm) in patients with normal Sao_2 (N Engl J Med 2017;13:1240-9; Circulation 2015;24:2143-50) • Supplemental oxygen considered if $Sao_2 < 90\%$, respiratory distress, or other high-risk features for hypoxemia

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425) *(continued)*

Predominant interventions on presentation/onset for stabilization – Any ACS	
Nitrates	• Can facilitate coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by increased venous capacitance • Nitroglycerin (NTG) 0.4 mg sublingually every 5 minutes for total of THREE doses; afterward, assess need for IV NTG • IV NTG is indicated in the first 48 hr after onset of ischemia, HF, or hypertension but should not preclude therapy such as β-blockers or ACE inhibitors when indicated **Should NOT be administered:** • If SBP < 90 mm Hg OR if SBP is > 30 mm Hg below baseline • If severe bradycardia (including heart block) with HR ≤ 50 beats/min • If tachycardia (HR ≥ 100 beats/min) in the absence of symptomatic HF • RV infarction, as evidenced by ischemic changes in inferior leads on ECG • If patient has received an oral phosphodiesterase inhibitor or riociguat within the past 24–48 hr
Aspirin	• Inhibits platelet activation • Four aspirin 81 mg each (324 mg total) or one 325 mg tablet (non–enteric coated) should be chewed and swallowed immediately
β-Blockade	• Decreases risk of ventricular arrhythmias and sudden cardiac death in early post-MI period • Decreases HR and myocardial oxygen demand and increases diastolic filling time of ventricles, thereby improving oxygen flow through the coronary arteries **β-Blockade should be initiated within the first 24 hr of an ACS unless:** • There are signs of HF • Active evidence of other shock states • If at increased risk of cardiogenic shock (SBP < 120 mm Hg, HR > 110 beats/min or < 60 beats/min, age > 70, and increased time since onset of symptoms) ***Relative contraindications* to β-blockade include:** • PR interval > 0.24 s, second- or third-degree heart block, and active asthma/reactive airway disease **Note: Intravenous β-blockers may be particularly harmful in patients with risk factors for shock.*
Other precautions	• Any NSAID other than aspirin should be avoided and/or discontinued for reasons beyond GI bleeding and nephrotoxicity, which may include reinfarction, hypertension, HF exacerbation, myocardial rupture, and overall increased risk of mortality associated with their use

ACS = acute coronary syndrome(s); GI = gastrointestinal; HF = heart failure; IV = intravenous; LMNOP = lasix-morphine-nitro-oxygen-position/positive pressure ventilation; NSAID = nonsteroidal anti-inflammatory drug; RV = right ventricular; Sao_2 = arterial oxygen saturation.

D. Revascularization
  1. Nonsurgical – Details of interventional cardiology procedures are too broad to be discussed in great detail in this chapter; however, the following are some considerations of the intervention that may play a role in post-procedural management during a left heart catheterization and percutaneous coronary intervention (PCI):
    a. Access site
      i. Radial artery (and, rarely, brachial artery) (Catheter Cardiovasc Interv 2011;78:840-6)
        (a) Easily accessible
        (b) Increased risk of vasospasm during procedure
        (c) Easily compressible vessel when hemostasis is needed post-procedure
        (d) Does not prevent patient mobility post-procedure
      ii. Femoral artery
        (a) Easily accessible
        (b) More difficult to compress vessel when hemostasis is needed post-procedure and also associated with increased bleeding complications
        (c) Limits patient mobility post-procedure for at least 12–24 hours (bleeding risk after sheath removal)
    b. Common interventions performed:
      i. Stent placement
        (a) Important to note the number of stents placed, types of stents, and locations of placement
        (b) Bare metal stent
          (1) Requires single antiplatelet therapy with either aspirin or a $P2Y_{12}$ antagonist for life and dual antiplatelet therapy (DAPT) for ideally 12 months after ACS, but shortened durations of at least 1 month may be considered for patients at high risk of bleeding
          (2) Longer therapies may be considered, depending on the number of stents and location(s) of the stent(s).
          (3) Higher risk of in-stent stenosis over time (because of neointimal cell proliferation)
        (c) Drug-eluting stent
          (1) Requires single antiplatelet therapy with either aspirin or a P2Y12 antagonist for life and DAPT for ideally 12 months after ACS, but shortened durations of at least 6 months may be considered for patients at high risk of bleeding longer or shorter therapy durations may be considered, depending on the number and/or location(s) of the stent(s) as well as patient bleeding risk. Some patients may benefit from a modified DAPT regimen, such as discontinuing aspirin after 1–3 months of DAPT and continuing with $P2Y_{12}$ inhibitor monotherapy for the remaining 9–11 months (Circulation 2022;145:e18-114). Of course, an individualized approach to DAPT duration is necessary.
          (2) The benefit of drug-eluting stents (i.e., everolimus, zotarolimus, biolimus) is the mitigation of in-stent restenosis, which is more common with bare metal stenting. However, the rate of stent endothelialization is also impaired such that the risk of stent thrombosis persists for a longer period. Consequently, drug-eluting stents mandate longer-term DAPT than bare metal stents.
      ii. Thrombectomy: Thrombus aspiration generally followed by stent placement at site of lesion
      iii. Percutaneous transluminal coronary angioplasty (PTCA), also called “plain old balloon angioplasty” (POBA): Balloon expansion and at least temporary displacement of occlusion at site of lesion

2. Surgical – Details of coronary artery bypass grafting (CABG) procedures, including conduit type and use of cardiopulmonary bypass (or performing off pump), are too broad to be discussed in greater detail in this chapter. According to the Society of Thoracic Surgeons/American College of Cardiology/American Heart Association (STS/ACC/AHA) CABG guidelines, emergency CABG is recommended in patients with an acute MI in the following scenarios (J Am Coll Cardiol 2011;58:e123-210):
    a. Primary PCI has failed or cannot be performed
    b. Coronary anatomy is more suitable for CABG
    c. Persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present
    d. Requirement of surgical repair of a postinfarction mechanical complication of MI (i.e., ventricular septal rupture, mitral valve insufficiency caused by papillary muscle infarction and/or rupture, or free wall rupture)
    e. Patients with cardiogenic shock who are suitable for CABG, irrespective of the time interval from MI to onset of shock and time from MI to CABG
    f. Patients with life-threatening ischemic ventricular arrhythmias in the presence of a left main stenosis of 50% or more and/or three-vessel CAD
    g. CABG use is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy.
    h. Early revascularization with PCI or CABG is reasonable for select patients older than 75 years with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock.
3. Medical management – No revascularization:
    a. Less invasive strategies may be opted for rather than revascularization in some patients. Considerations reinforce a patient-centered approach driven by evidence of ongoing/recurrent ischemia and feasibility of revascularization, including myocardial viability, patient frailty, and comorbid disease states.
    b. Ongoing care outlined in section E remains the focus of optimizing aggressive medical management.

E. Antithrombotics in MI
1. The roles and combinations of antithrombotics continue to be refined in select populations (those with NSTEMI/ACS, STEMI, and PCI). For the most current guidelines and landmark trials, please see www.acc.org/guidelines.
2. Oral antiplatelet therapy
    a. Platelets can be activated by several different mechanisms, only some of which can be inhibited by medications.
    b. Clopidogrel had previously been the standard of care P2Y12 inhibitor but has fallen out of favor in ACS because of its slow onset of action, variable platelet inhibition because of genetic polymorphisms (*CYP2C19*), drug interactions, and delayed onset of action, leading to an increased risk of inadequate antiplatelet response or bleeding complications. Clopidogrel may still be used in patients who are medically managed for ACS, in those receiving stents for non-ACS indications, among patients at high risk of bleeding, those maintained on concomitant anticoagulation and when cost of other $P2Y_{12}$ inhibitors is prohibitive.

c. Evaluation of antiplatelet therapy can be performed with platelet function testing and/or genotyping. However, neither is currently recommended routinely in the clinical setting. Clinical outcomes with the use of platelet function testing to modify antiplatelet therapy (ie, high-dose vs standard-dose clopidogrel) in patients undergoing PCI with high on-treatment platelet reactivity have been negative to date (*JAMA*. 2011;305(11):1097-1105). Outcomes with prospective genotype-guided antiplatelet therapy (*CYP2C19*) from large cohorts of patients undergoing PCI have shown lower rates of major adverse cardiovascular events and lower rates of bleeding (*JACC Cardiovasc Interv*. 2018;11(2):181-191; *J Am Coll Cardiol*. 2018;71(17):1869-1877; *N Engl J Med*. 2019;381(17):1621-1631).

d. Platelet Inhibition and Patient Outcomes (PLATO) trial: Compared ticagrelor with clopidogrel in patients with ACS. Ticagrelor showed a significant reduction in cardiovascular death, MI, and stroke without increasing the risk of major bleeding compared with clopidogrel (*N Engl J Med*. 2009;361(11):1045-1057).

e. Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) trial: Evaluated prasugrel compared with clopidogrel in patients with ACS undergoing PCI. Prasugrel was superior in reducing ischemic events but had a higher risk of major bleeding, particularly in patients with a history of stroke or TIA (*N Engl J Med*. 2007;357:2001-2015).

f. Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial: Compared prasugrel and ticagrelor in patients with ACS treated invasively. Prasugrel was more effective in reducing the composite of death, MI, or stroke, with a bleeding risk similar to ticagrelor (*N Engl J Med*. 2019;381(16):1524-1534).

g. The response to antiplatelets that require hepatic biotransformation for activation (clopidogrel and prasugrel) can be altered in patients with liver dysfunction, patients with cardiogenic shock, or those undergoing therapeutic hypothermia because of the delay in gut absorption and isoenzyme activity. In other situations, such as when enteral administration is not an option, parenteral antiplatelets may be considered (Table 5). These options include glycoprotein IIb/IIIa inhibitors and cangrelor, which have been studied primarily in the setting of PCI but have data supporting their use as bridging agents.

Table 4. Oral Antiplatelet Therapy (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of action	Inhibits thromboxane A_2–mediated platelet activation	Inhibits ADP-mediated platelet activation at $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at $P2Y_{12}$ receptor
Loading dose	162–325 mg	300 mg for medical management 600 mg for invasive management	60 mg	180 mg
Maintenance dose	81 mg daily	75 mg daily	5–10 mg daily[a]	90 mg BID
Route	Oral	Oral	Oral	Oral
Prodrug	No	Yes	Yes	No
Reversible platelet binding	No	No	No	Yes

Table 4. Oral Antiplatelet Therapy (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57) *(continued)*

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Onset	30 min	2–6 hr	30 min	30 min
% Platelet inhibition	~ 10–20	30–40	60–70	60–70
Recommended holding duration before CABG[b]	Do not hold	5 days	7 days	3 days
Other notable adverse effect(s) or clinical pearls		Pharmacogenomic variability (CYP2C19) in response is well documented	Contraindication in patients with any history of stroke or TIA, and warning for use in patients ≥ 75 y or weight < 60 kg because of bleeding risk	• Adenosine-induced dyspnea and bradyarrhythmias • Older adult patients and patients with moderate or severe hepatic impairment may be at increased risk of bleeding

[a]Patients with lean body weight (< 60 kg) should receive a 5 mg daily maintenance dose of prasugrel

[b]Decisions to hold these agents before other invasive procedures must consider indications for use, risk of thrombosis (i.e., stent type, locations, and number), and risk of bleeding associated with intended procedure/surgery (JAMA 2013;310:1451-2; Catheter Cardiovasc Interv 2013;82:1113-4; JAMA 2013;310:189-98; N Engl J Med 2013;368:2113-24; J Am Coll Cardiol 2011;58:e44-122; Reg Anesth Pain Med 2010;35:64-101; J Am Coll Cardiol 2007;49:734-9).

ADP = adenosine diphosphate; BID = twice daily; TIA = transient ischemic attack.

3. Parenteral antithrombotics
    a. Use of these agents is most concentrated in the procedural setting, although use may continue for a finite period post-procedurally.
    b. The selection and use among the agents in Table 5 may depend on presentation, timing/dose of pre-procedural antiplatelet medication administration, clot burden during procedure, and estimated bleeding risk of the procedure.

Table 5. Parenteral Antithrombotics (Circulation 2014;130:e344-426; Circulation 2013;127:e362-425;Circulation 2015;131:1123-49; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Heparin (UFH)[a]	Bivalirudin	Eptifibatide	Tirofiban	Cangrelor[b]
Mechanism of action	Indirect thrombin inhibition (binds to antithrombin III)	Direct thrombin inhibitor	Binds to GP IIb/IIIa platelet receptor, inhibiting final common pathway for platelet aggregation	Binds to GP IIb/IIIa platelet receptor, inhibiting final common pathway for platelet aggregation	Inhibits ADP-mediated platelet activation at $P2Y_{12}$ receptor
Bolus dose	50–100 units/kg based on target activated clotting time (ACT)	0.75 mg/kg	180 mcg/kg x 2, 10 min apart	25 mcg/kg	30 mcg/kg
Continuous infusion	Not typically given during PCI	1.75 mg/kg/hr	2 mcg/kg/min	0.15 mcg/kg/min	4 mcg/kg/min
Platelet inhibition	Indirectly inhibits thrombin-mediated platelet activation	Indirectly inhibits thrombin-mediated platelet activation	Restoration of platelet function within 6–8 hr of discontinuation	Restoration of platelet function within 6–8 hr of discontinuation	Onset of platelet inhibition within min of administration Restoration of platelet function within 1 hr of discontinuation
Elimination	Hepatic and reticulo-endothelial system	80% plasma proteolysis 20% renal	Renal (50%)	Renal (65%)	Plasma dephosphorylation
Removed by dialysis	No	Partial	Yes	Yes	N/A
Other notable adverse effect(s) or clinical pearls	Target ACT of about 200–300 s during procedure based on presence of GP IIb/IIIa inhibitor and device used	Requires renal dose adjustment Useful in patients with suspected or confirmed HIT May be preferred in patients with higher bleeding risk (particularly compared with UFH with GP IIb/IIIa inhibitor and among patients who undergo a transfemoral PCI approach)	Requires renal dose adjustment Acute, profound thrombocytopenia	Requires renal dose adjustment Acute, profound thrombocytopenia	Oral prasugrel and clopidogrel must be given immediately after discontinuation of cangrelor infusion to maintain platelet inhibition. Ticagrelor should be given as soon as possible, and administration may overlap with cangrelor infusion to maintain platelet inhibition after cessation of cangrelor

[a] Enoxaparin may be used as an alternative to UFH.

[b] U.S. Food and Drug Administration (FDA) approved as an adjunct to PCI for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not receiving a glycoprotein IIb/IIIa inhibitor.

ACT = activated clotting time; GP = glycoprotein; HIT = heparin-induced thrombocytopenia; N/A = not applicable; UFH = unfractionated heparin.

F. Post-Intervention Complications
   1. Bleeding (particularly retroperitoneal bleeding)
      a. Several antithrombotic agents are used during PCI to inhibit both the platelets and the clotting cascade, causing potential coagulopathies.
      b. In addition to antithrombotic use, the catheterization access site has been identified as a major contributor to post-PCI bleeding complications.
   2. Dissection/rupture of free wall, coronary artery, or aorta: Although this may be spontaneous, it may also be caused by vessel trauma from the catheter itself.
   3. Stent thrombosis
      a. When antiplatelet therapy is discontinued early (aspirin, $P2Y_{12}$ inhibitor, or both), stent thrombosis may occur in up to 25% of coronary artery stents, irrespective of type of stent (drug-eluting stent or bare metal stent).
      b. Almost 1 in 7 patients may discontinue $P2Y_{12}$ inhibitors within 30 days post-PCI, thus increasing mortality risk (adjusted hazard ratio [HR] 9.0; 95% confidence interval [CI], 1.3–60.6) (JAMA 2013;310:189-98).
      c. Mortality rates associated with stent thrombosis can be as high as 45%.
      d. Despite bleeding risks in critically ill patients, careful consideration should be given to correlating these risks with the risk of stent thrombosis.

G. Mechanical complications after MI: Most often the result of a large, proximal MI or in patients who present late after the initial insult occurs, resulting in extensive myocardial damage:
   1. Free wall rupture (most often a fatal complication)
   2. Papillary muscle rupture causing acute mitral regurgitation
   3. Dressler syndrome pericardial effusion
   4. Post-MI ventricular septal defect (associated with up to 50% mortality; repair must be delayed for optimal outcomes because the tissue is too friable to repair)
   5. LV aneurysm
   6. Arrhythmias (particularly after reperfusion)

H. Ongoing Care – Quality measures for NSTEMI or STEMI independent of revascularization or medical management
   1. Medications that should be initiated before discharge or contraindications should be documented in the medical record:
      a. Aspirin
      b. Statin (high intensity)
      c. $P2Y_{12}$ inhibitor
      d. β-Blocker
      e. If LVEF less than or equal to 40%
         i. ACE inhibitor or ARB or angiotensin receptor/neprilysin inhibitor
         ii. Aldosterone antagonist (if also evidence of HF and/or diabetes)
         iii. Sodium glucose co-transporter 2 inhibitor (if patient has other compelling indications such as diabetes or chronic kidney disease)
   2. Interventions and/or referrals
      a. LV function assessment (by imaging or during catheterization)
      b. Cardiac rehabilitation
      c. Smoking cessation counseling
      d. Measurement of a lipid profile, including the low-density lipoprotein (LDL) cholesterol, should preferably be obtained within 24 hours of admission. Any lipid profile measured between 6 months before first medical contact and hospital discharge qualifies for this quality measure.
   3. For more information on cardiology-related quality measures and registries, see www.ncdr.com.

Patient Case *(Continued)*

4. J.M.’s ECG results reveal no acute evidence of ST segment changes. However, the resident is still considering a diagnosis of ACS, given the patient’s shortness of breath and mild troponin elevation. Which statement would be most accurate regarding the potential for other potential diagnoses?
    - A. No, this is most likely an NSTEMI.
    - B. Yes, it is likely undiagnosed chronic obstructive pulmonary disease.
    - C. Yes, it is likely early sepsis.
    - D. Yes, it is likely decompensated HF.

5. J.M. has been experiencing intermittent bradycardia on telemetry. The team has consulted the cardiac electrophysiology team. In the meantime, which statement most accurately reflects whether any other underlying correctable/contributing causes can be addressed?
    - A. Ticagrelor could be discontinued and switched back to clopidogrel.
    - B. Ticagrelor should be discontinued altogether.
    - C. No treatment intervention is needed; this is likely the result of J.M.’s HF progression.
    - D. J.M.’s hyperkalemia should be treated.

V. ARRHYTHMIAS AND ANTIARRHYTHMICS

A. Pathophysiology: Arrhythmias are generally caused by 2 main mechanisms:
  1. Abnormal impulse formation
    a. Altered automaticity
    b. Abnormal automaticity
    c. Triggered activity—early or delayed
  2. Abnormal impulse conduction
    a. Reentry
    b. Conduction block

B. Bradyarrhythmias (beyond sinus) and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8)
  1. Etiologies of heart block (Box 3)

Box 3. Causes of Bradyarrhythmias

- CAD
- Degenerative conduction disease
- Drug induced
- Electrolyte disturbances (particularly hyperkalemia)
- Endocarditis
- Myocarditis
- Surgery (particularly cardiac surgery)
- Tumors
- Vagus nerve–mediated heart block

CAD = coronary artery disease.

2. When evaluating ECGs in the presence of heart block, QRS complex evaluation can guide some differential diagnoses to the source of conduction problems (see Table 6).
   a. Narrow QRS complexes commonly indicate AV nodal dysfunction.
   b. Wide QRS complexes may indicate dysfunction in either the AV node or the His-Purkinje system.

Table 6. Bradyarrhythmias and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8)

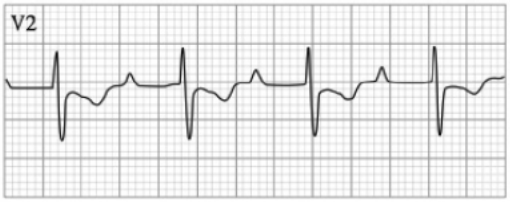
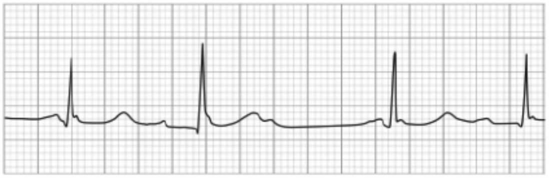
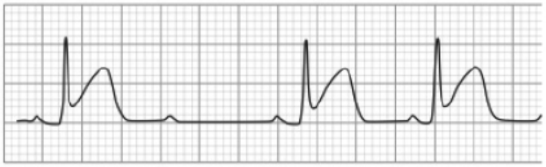
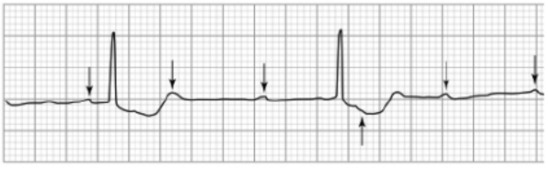
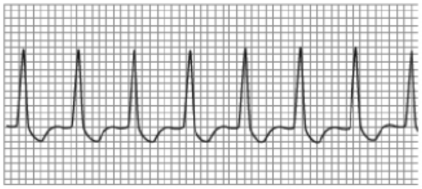
Type	ECG Example	Description
First degree		Delayed conduction from the sinoatrial (SA) node to the atrioventricular (AV) node characterized by a P-R interval > 0.2 s (1 big box on the ECG strip) Relatively benign; however, underlying contributors should be evaluated and minimized (i.e., β-blockers and other AV nodal blocking agents)
Second-degree Mobitz type 1 (Wenckebach)		Consistent P-P interval with progressive prolongation of the P-R (indicating impaired SA to AV node conduction) eventually resulting in absence of a QRS complex because of the lack of AV node conduction of atrial impulse Of most concern in older adult patients in whom this may be indicative of progressive conduction disease; may be more benign in younger patients “Longer, longer, longer, drop … must be Wenckebach”
Second degree Mobitz type 2		Consistent P-P interval and consistent P-R interval duration with spontaneous absence of a QRS complex because of the lack of AV node conduction of atrial impulse Usually indicative of more significant conduction disease and associated with syncope, HF, and increased mortality rates
Third degree (Complete heart block)		Characterized by consistent P-P intervals, consistent R-R intervals, and variable/random P-R interval representing independent, uncoordinated atrial and ventricular conduction (A-V dissociation). The arrows on this ECG strip identify P waves, showing regular P-P interval with varying P-R interval

Table 6. Bradyarrhythmias and Types of Heart Block (Critical Care Medicine 2014:xix; Pathophysiology of Heart Disease 2011:xiv; BMJ 2002;324:662-5; BMJ 2002;324:415-8) *(continued)*

Type	ECG Example	Description
Junctional rhythm		Manifested when sinus node dysfunction allows the AV node to take over as the active cardiac pacemaker, resulting in retrograde conduction through the atria

3. Management of bradyarrhythmias includes three principal strategies (see also Figure 8). Stabilize the patient, if symptomatic.
   a. Consider atropine for temporary correction to decrease vagal tone. Note that the recommended dose of atropine is 1 mg, which can be given every 3–5 minutes for a maximum of 3 mg.
   b. Consider pacing strategies (temporary transvenous pacer, transcutaneous pacer, pacing pulmonary artery catheter). Interrogate permanent pacemaker for malfunction/optimization.
   c. Consider chronotropic β-agonist infusion.
      i. Dopamine
      ii. Epinephrine
      iii. Isoproterenol
      iv. Dobutamine (if blood pressure normal or elevated)
   d. Identify and treat underlying causes/toxidromes.

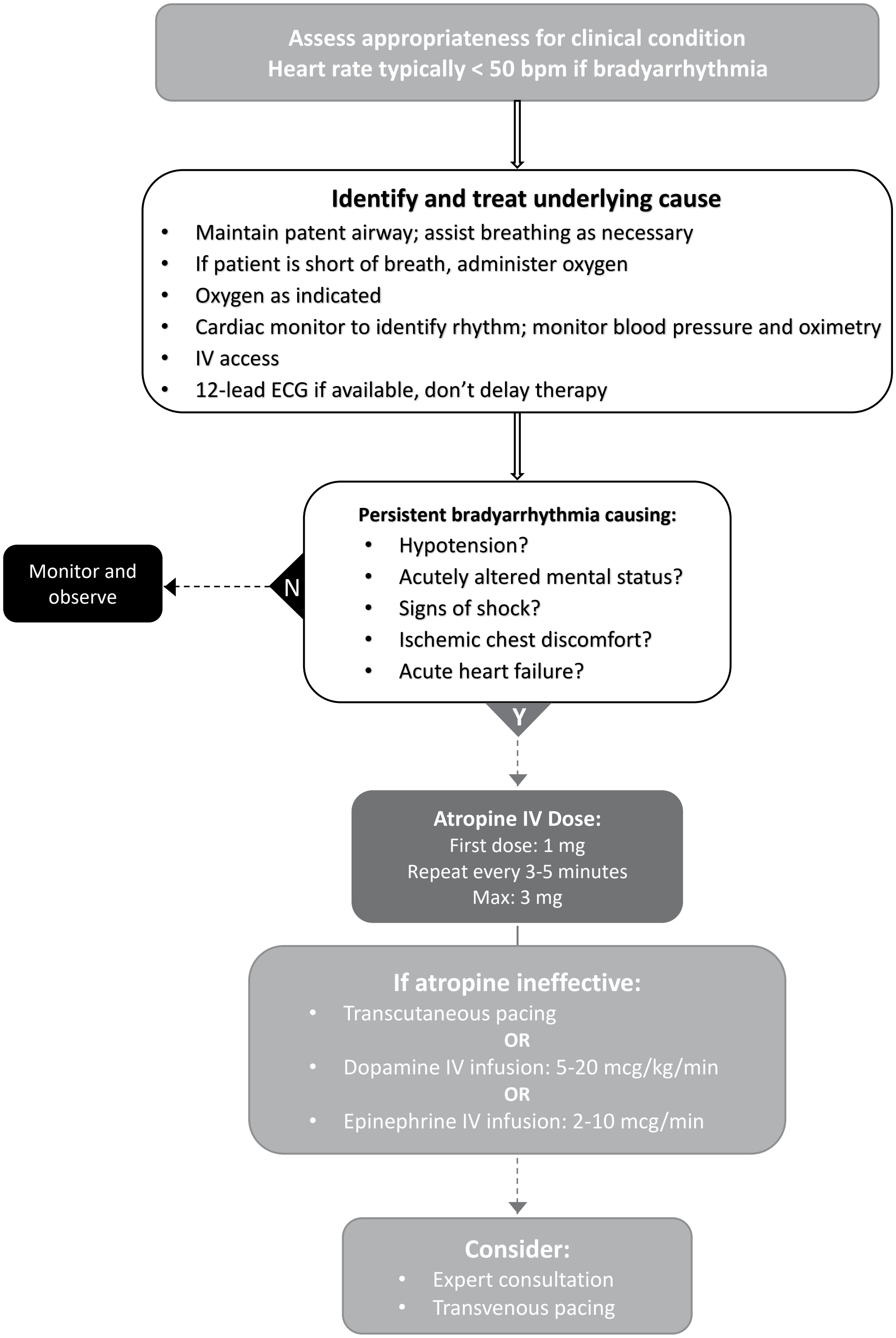

Assess appropriateness for clinical condition
Heart rate typically < 50 bpm if bradyarrhythmia
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• If patient is short of breath, administer oxygen
• Oxygen as indicated
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
• IV access
• 12-lead ECG if available, don't delay therapy
Persistent bradyarrhythmia causing:
• Hypotension?
• Acutely altered mental status?
• Signs of shock?
• Ischemic chest discomfort?
• Acute heart failure?
N
Monitor and observe
Y
Atropine IV Dose:
First dose: 1 mg
Repeat every 3-5 minutes
Max: 3 mg
If atropine ineffective:
• Transcutaneous pacing
OR
• Dopamine IV infusion: 5-20 mcg/kg/min
OR
• Epinephrine IV infusion: 2-10 mcg/min
Consider:
• Expert consultation
• Transvenous pacing

Figure 8. Advanced cardiac life support bradycardia algorithm adapted from the 2020 American Heart Association guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Circulation 2021;142(14_suppl_2):S366-468).

C. Tachyarrhythmias (beyond sinus) – Etiologies and hemodynamic consequences
  1. Etiologies of tachyarrhythmias
    a. Usually related to enhanced automaticity, reentry, or triggered activity
    b. A history that includes ischemic heart disease or congestive cardiac failure is 90% predictive of VT.
  2. In evaluating ECGs for tachyarrhythmias, some fundamental considerations include:
    a. Evaluate for the presence of P waves.
    b. Evaluate the width of the QRS complex.

Table 7. Tachyarrhythmias (beyond sinus)[a] (Circulation 2014;130:2071-104; BMJ 2002;324:594-7776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93; J Am Coll Cardiol 2018;72:1677-749)

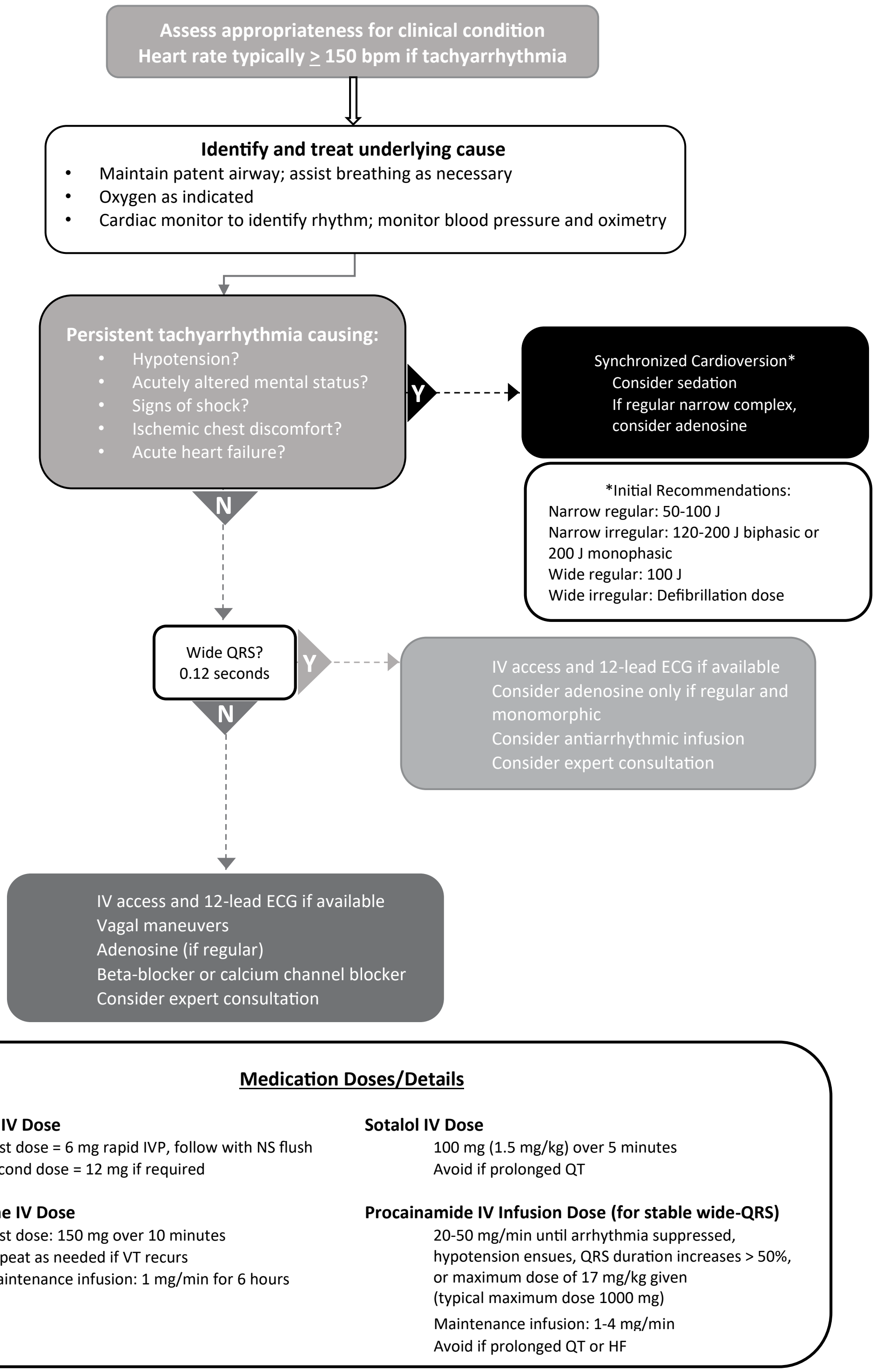
Supraventricular Tachyarrhythmias				
Type	**Rhythm**	**P-wave Attributes**	**Atrial Rate (beats/min)**	**Description**
Premature atrial complexes (PACs)	Irregular	N/A	N/A	Generally benign but may be more evident with increased sympathetic tone, stress, and pericarditis or with sympathomimetic use In some cases, can lead to an AV block or initiate a reentrant supraventricular tachycardia (SVT) or AF
Supraventricular tachycardia (SVT)	Regular	Hidden or can be retrograde	140–250	Usually sudden onset/offset with narrow QRS complexes Often caused by reentry within the atrium or AV node or by an accessory conduction pathway Can be subcategorized as: AV nodal reentrant tachycardia (AVNRT) AV reentrant tachycardia (AVRT) Sinus node reentry tachycardia
Atrial flutter (AFl)	Regular	Saw-tooth appearance	180–350	Generally conducts through the ventricles in a 2:1 fashion, resulting in ventricular rates of 100–150 beats/min In some scenarios, slowing the atrial rate may increase the number of conducted beats, leading to rapid ventricular rates and potential hemodynamic compromise Associated with increased risk of stroke
Atrial fibrillation (AF)	Irregular	No distinct P wave visible	Unable to determine	Most common arrhythmia, characterized by irregular ECG appearance because of multiple reentry circuits and ectopic foci ("irregularly irregular") Often associated with structural heart disease and potentiated by increased left atrial pressures among other influencing contributors such as age, inflammation, and sympathetic tone Associated with increased risk of stroke

Table 7. Tachyarrhythmias (beyond sinus)[a] (Circulation 2014;130:2071-104; BMJ 2002;324:594-7776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93; J Am Coll Cardiol 2018;72:1677-749) *(continued)*

<table>
<tr><th colspan="5">Supraventricular Tachyarrhythmias</th></tr>
<tr><th>Type</th><th>Rhythm</th><th>P-wave Attributes</th><th>Atrial Rate (beats/min)</th><th>Description</th></tr>
<tr><td>Multifocal atrial tachycardias (MATs)</td><td>Irregular</td><td>> 3 different types of distinct P waves</td><td>100–130</td><td>Can be misdiagnosed as AF
Commonly associated with respiratory disease, HF, critical illness
May be exacerbated by electrolyte abnormalities or toxicity with digoxin or theophylline</td></tr>
<tr><th colspan="5">Ventricular Arrhythmias</th></tr>
<tr><th colspan="2">Type</th><th colspan="3">Description</th></tr>
<tr><td colspan="2">Premature ventricular complexes (PVCs)</td><td colspan="3">Results from an ectopic ventricular focus conduction that can be identified by the lack of a preceding P wave. Commonly benign or asymptomatic but may be of concern if present in patterns or in patients with advanced heart disease
Bigeminy: Every other beat is a PVC
Trigeminy: Every third beat is a PVC
Couplets: Patterns of two consecutive PVCs
Triplets: Patterns of three consecutive PVCs</td></tr>
<tr><th colspan="5">Ventricular Arrhythmias</th></tr>
<tr><th colspan="2">Type</th><th colspan="3">Description</th></tr>
<tr><td colspan="2">Ventricular tachycardia (VT)</td><td colspan="3">Potentially lethal wide QRS complex tachycardia characterized according to morphology and duration; can degenerate into ventricular fibrillation (VF) or asystole
<i>Monomorphic VT:</i> When every QRS complex appears the same and the rate is regular (100–200 beats/min); commonly caused by reentry circuit related to myocardial scar or fibrosis
<i>Polymorphic:</i> When the QRS complexes continually vary in shape and rate; most commonly caused by myocardial ischemia, but other causes include multiple ectopic foci or torsades de pointes from QT prolongation.
<i>Non-sustained VT:</i> Self-terminating episodes lasting for < 30 s
<i>Sustained VT:</i> If VT persists for more than 30 s, produces severe symptoms, including syncope, or requires termination by administration of an antiarrhythmic drug or direct cardioversion/defibrillation
VT storm: ≥ 3 episodes of sustained VT in a 24-h period</td></tr>
<tr><td colspan="2">Ventricular fibrillation (VF)</td><td colspan="3">Life-threatening arrhythmia with a chaotic ECG with no discernible QRS, representing rapid disorganized conduction with no resultant coordinated ventricular contractions</td></tr>
</table>

[a] Other arrhythmias beyond the scope of this review include sick sinus syndrome (tachy-brady syndrome).

3. Management of tachyarrhythmias with a pulse includes the following strategies:
   a. Stabilization of patient: See Figure 9
      i. Atrial tachyarrhythmias
         (a) Heart rate control typically with class II agents, class IV agents, and/or digoxin (see Appendix A)


Assess appropriateness for clinical condition
Heart rate typically ≥ 150 bpm if tachyarrhythmia
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• Oxygen as indicated
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
Persistent tachyarrhythmia causing:
• Hypotension?
• Acutely altered mental status?
• Signs of shock?
• Ischemic chest discomfort?
• Acute heart failure?
Y
Synchronized Cardioversion*
Consider sedation
If regular narrow complex, consider adenosine
*Initial Recommendations:
Narrow regular: 50-100 J
Narrow irregular: 120-200 J biphasic or 200 J monophasic
Wide regular: 100 J
Wide irregular: Defibrillation dose
N
Wide QRS?
0.12 seconds
Y
IV access and 12-lead ECG if available
Consider adenosine only if regular and monomorphic
Consider antiarrhythmic infusion
Consider expert consultation
N
IV access and 12-lead ECG if available
Vagal maneuvers
Adenosine (if regular)
Beta-blocker or calcium channel blocker
Consider expert consultation

Medication Doses/Details

Adenosine IV Dose
First dose = 6 mg rapid IVP, follow with NS flush
Second dose = 12 mg if required

Amiodarone IV Dose
First dose: 150 mg over 10 minutes
Repeat as needed if VT recurs
Maintenance infusion: 1 mg/min for 6 hours

Sotalol IV Dose
100 mg (1.5 mg/kg) over 5 minutes
Avoid if prolonged QT

Procainamide IV Infusion Dose (for stable wide-QRS)
20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases > 50%, or maximum dose of 17 mg/kg given (typical maximum dose 1000 mg)
Maintenance infusion: 1-4 mg/min
Avoid if prolonged QT or HF

Figure 9. Advanced cardiac life support tachycardia algorithm adapted from the 2020 American Heart Association guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Circulation 2021;142(16_suppl_2):S366-468).

        - (b) Heart rhythm control
            - (1) Antiarrhythmic therapy typically with class Ic or class III agents (see Appendix A)
            - (2) Synchronized electrical cardioversion
            - (3) Catheter-based ablation
            - (4) Surgical ablation
    - ii. Ventricular tachyarrhythmias
        - (a) Catheter ablation
        - (b) Antiarrhythmic therapy
        - (c) Evaluation for implantable cardioverter-defibrillator
- b. Overall considerations for antiarrhythmics (see Appendix A) (Circulation 2014;130:2071-104; Heart Fail Rev 2014;19:285-93; Circulation 2012;125:381-9; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4)
    - i. Abrupt discontinuation of chronic antiarrhythmics (i.e., chronic medication before ICU admission) should be done with caution and awareness of antiarrhythmic indication as well as risks-benefits of continuation/cessation.
    - ii. Appropriate monitoring and potential adjustment may be warranted with many of these agents in the critically ill patient.
        - (a) QT/QTc prolongation increases the risk of Torsades de pointes. This risk can be influenced not only by the absolute duration of the QT/QTc but also by the rate at which the QT/QTc is changed (i.e., faster change may also increase risk).
        - (b) The class III antiarrhythmics sotalol and dofetilide can be used for a variety of arrhythmias (most notably AF/AFl) and, because of some notable characteristics, should be watched closely when used in the critically ill patient.
            - (1) Both are renally eliminated.
            - (2) Both have notable interactions with several other medications (especially dofetilide on the basis of CYP3A4 and renal transport) in addition to their effect on the QT/QTc interval.
            - (3) ECG, electrolytes, and renal function monitoring should be performed for safety and tolerability 2–3 hours after the first five doses when initiating, reinitiating, or introducing another interacting or QT-prolonging agent.
            - (4) Electrolyte abnormalities may place a patient at increased risk of Torsades de pointes (particularly magnesium and potassium).
            - (5) Dofetilide is particularly useful among patients with structural heart disease (including HF) because of a neutral effect on mortality. In contrast, sotalol has been associated with increased mortality in patients with HF and is not recommended in this patient population for atrial arrhythmias.
        - (c) If a patient develops Torsades de pointes, the patient should be managed with the following:
            - (1) Intravenous magnesium 2-g rapid infusion
            - (2) Discontinuation of any offending medications contributing to QT prolongtion
            - (3) Pharmacologic pacing with beta agonists (i.e., isoproterenol, dobutamine, epinephrine, dopamine); bradycardia increases the risk for TdP, so increasing HR can help prevent future events
            - (4) Correction of electrolyte disturbances such as hypokalemia
            - (5) Temporary pacing to increase heart rate

    - iii. Common agents in the ICU used to treat tachyarrhythmias
        - (a) β-Blockers
            - (1) May be of limited use in patients receiving vasopressors and/or inotropes, but can be used for both atrial and ventricular tachyarrhythmias

(2) Esmolol has the shortest half-life (cleared by plasma esterases), and administration rates commonly coincide with high volumes of fluid.

(3) Agents with combined α_1-antagonism and nonselective β-antagonism will have greater effects on blood pressure than their β_1-specific antagonist counterparts.

- β_1-specific antagonist examples:
  - Esmolol (intravenous), metoprolol tartrate (oral/intravenous)
- Agents with combined α_1- and nonselective β-antagonism effects include:
  - Carvedilol (oral) – about 25:1 ratio of $\beta:\alpha_1$ receptor activity
  - Labetalol (intravenous) – about 7:1 ratio of $\beta:\alpha_1$ receptor activity
  - Labetalol (oral) – about 3:1 ratio of $\beta:\alpha_1$ receptor activity

(b) Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)

(1) Not recommended in patients with HFrEF because of potent negative inotropic effects (class III C). (J Am Coll Cardiol 2013;62:e147-239)

(2) May be of limited use in patients on vasopressors and/or inotropes, but can be used for atrial tachyarrhythmias

(c) Amiodarone

(1) Commonly used for both atrial and ventricular tachyarrhythmias

(2) Demonstrated safety in patients with structural heart disease (HF) because of neutral effect on mortality

(3) Affects all phases of the action potential (sodium [Na], calcium [Ca], potassium [K] channel and provides some α- and β-antagonism)

(4) Severe hypotension can occur with intravenous amiodarone because of the solvent polysorbate 80 (Tween 80) used in some formulations. This transient hypotension in patients with a pulse can be associated with rapid infusions, particularly of undiluted drugs, and is best avoided by dilution and slower administration. However, in pulseless patients, rapid intravenous administration of undiluted amiodarone is commonly indicated.

(5) Among common agents used in the ICU, amiodarone has one of the largest volumes of distribution (about 60 L/kg) and prolonged half-lives (about 35–110 days).

(6) In adults, common total intravenous or oral loading doses throughout several days are about 8–10 g before switching to a maintenance dose.

$$\text{Loading dose} = \text{concentration} \times \text{volume of distribution} \times \text{weight}$$
$$7.2\text{–}12\text{ g} = (1.5\text{–}2.5\text{ mg/L}) \times (60\text{ L/kg}) \times (80\text{ kg})$$

(7) Extensive metabolism by CYP3A4 and CYP2C8 and enzyme inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6, resulting in several drug-drug interactions ((e.g., warfarin, statins)

(8) If patients are to be continued on amiodarone for a prolonged duration, thyroid and liver function tests, pulmonary function tests, chest radiographs, and ophthalmic examinations should be evaluated periodically (Heart Rhythm 2007;4:1250-9).

(d) Lidocaine

(1) Indicated only for treatment of ventricular tachyarrhythmias and is particularly useful if the tachyarrhythmia is caused by active ischemic myocardial tissue

(2) Efficacy and toxicity are both concentration dependent.

(3) Metabolism is largely dependent on hepatic blood flow; the primary metabolites are monoethylglycinexylidide (MEGX) and glycine xylidide (GX) and are mediated by CYP1A2. Both lidocaine and MEGX contribute to therapeutic effect and toxicity, whereas GX has predominantly toxic adverse effects. Lidocaine's metabolites are eliminated renally.

(4) Concentration-dependent protein binding includes about 25% bound to albumin and about 50% bound to α_1-acid glycoprotein (AAG).

(5) As AAG increases and decreases as an acute-phase reactant within the first 12–72 hours after certain stresses (e.g., acute MI, HF exacerbation, trauma), an unsuspected variation can occur in free lidocaine concentrations. Because of the toxicity profile and concentration-dependent efficacy, routine concentrations should be monitored in most patients if lidocaine is to be continued beyond 24 hours (particularly in patients with advanced age, HF, liver disease, and renal dysfunction).

Table 8. Lidocaine Concentrations and Toxicity Symptoms

Total Serum Concentration (mg/L)	Toxicity
< 1.5–5	Typical therapeutic goal concentration
> 5–8	Increasing risk of light-headedness, confusion, dizziness, tinnitus, twitching, tremor, blurred or double vision, hypotension, and bradycardia
> 8	High risk of seizures, respiratory depression, hypotension, bradycardia, AV nodal blockade, decreased cardiac output

AV = atrioventricular.

(e) Procainamide

(1) Indicated for the treatment of hemodyanmically stable, sustained, monomorphic VT and atrial fibrillation with pre-excitation (*Circulation*. 2017;138 (13):e272-391; *Circulation*. 2024;149(1):e1-156)

(2) Compared to amiodarone, procainamide has been shown to be more effective at terminating monomorphic VT with fewer cardiac complications (Eur Heart J 2017;38:1329-35).

(3) Procainamide should be avoided in patients with severe HF, acute MI, and end-stage renal disease.

(4) Procainamide is a sodium channel blocking antiarrhythmic, so close monitoring because of the QRS complex is necessary during treatment. Procainamide should be discontinued if the QRS widens by more than 50%.

(5) Close monitoring of the QT/QTc is also important because both procainamide and its active metabolite, N-acetyl procanamide, have potassium channel blocking properties.

(f) Digoxin

(1) Digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe LV dysfunction and HF or hemodynamic instability (Circulation 2019;140:e125-51).

(2) Use for AF should be done with caution. Two published retrospective trials have shown considerable evidence for increased hospitalization rates and risk of death.

- 71% increased risk of death (HR 1.71; 95% CI, 1.52–1.93) and 63% increased risk of hospitalization (HR 1.63, 95% CI, 1.56–1.71) (Circ Arrhythm Electrophysiol 2015;8:49-58)
- Digoxin-treated patients had higher mortality rates (95 vs. 67 per 1000 person-years; $p<0.001$), and use was independently associated with mortality, despite multivariate adjustment (HR 1.26; 95% CI, 1.23–1.29, $p<0.001$) (J Am Coll Cardiol 2014;64:660-8).

- Eliminated renally; thus, may pose risks of digoxin toxicity in patients with acute or chronic renal failure

(3) Although the volume of distribution is relatively large (7–10 L/kg in healthy adults), only a small percentage of total body stores are present in the serum.

(4) Digoxin has a smaller volume of distribution in patients with renal failure (around 4.5 L/kg); thus, loading doses may be lower in these patients.

(5) Digoxin efficacy and toxicity do not correlate well with drug concentrations.

- Common therapeutic targets for heart rate control are 0.8–1.5 ng/mL, although many clinical laboratories report therapeutic concentrations within 0.5–2.0 ng/mL. For patients with HFrEF, the recommended serum concentration is 0.5−0.9 ng/mL
- Toxicity, which can present at any serum concentration, should be evaluated according to clinical manifestations, including: nausea, vomiting, anorexia, mental status changes, visual disturbances, ventricular arrhythmias, bradycardia, and hyperkalemia.
- Efficacy is largely based on clinical control of the heart rate; steady-state concentrations (more than 5–7 days after initiation) are typically used only to validate that concentrations are not supratherapeutic.

4. Anticoagulation for AF or atrial flutter

a. According to the 2023 ACC/AHA/ACCP/HRS Guideine for the Diagnosis and Management of Atrial Fibrillation Guidelines all patients with atrial flutter or paroxysmal, persistent, or permanent AF should be evaluated for anticoagulation, preferably using the CHA_2DS_2-VASc score to approximate stroke risk (Circulation 2024;149:e1-156).

i. For a CHA_2DS_2-VASC score of 2 or greater in men and 3 or greater in women, an oral anticoagulant is recommended (J Am Coll Cardiol 2019;12:104-32).

ii. It is reasonable to omit anticoagulation in patients with a CHA_2DS_2-VASc score of 0 in men or 1 in women. Antiplatelet therapy is not recommended for stroke prevention in atrial fibrillation patients, even in those who are low risk.

iii. For patients with AF and a mechanical prosthetic heart valve or valves, warfarin anticoagulation and international normalized ratio (INR) goals should be consistent with the type and location of the prosthetic valve. Bridging is no longer routinely recommended (Chest 2022;165:1127-39). Bridging with unfractionated heparin can be considered in those at high risk for thromboembolic events, including:

(a) Older generation mechanical valves (e.g., tilting-disc valve)

(b) A mechanical mitral valve with one or more other risk factors for thromboembolism

(c) A recent thromboembolic event in preceding 3 months

(d) History of a perioperative thromboembolism

iv. In patients with AF at intermediate risk for thromboembolism (average $CHADS_2$ score of 2-3), the use of bridging with low-molecular-weight heparin was non-inferior to no bridging for elective procedures. However, there was a significant excess of major bleeding in the low-molecular-weight heparin group. Note that patients with a mechanical valve or stroke/transient ischemic attack/systemic embolism within the preceding 12 weeks were not eligible for inclusion in the study (N Engl J Med 2015;373:823-33).

v. Although the $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used to estimate annual stroke risk, these scoring systems were not founded in the context of critically ill patients.

Table 9A. CHADS$_2$ Stroke Risk Score in AF

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stroke Rate, %
CHADS$_2$			
Congestive heart failure	1	0	1.9
Hypertension	1	1	2.8
Age ≥ 75	1	2	4.0
Diabetes	1	3	5.9
Stroke/TIA/thromboembolism	2	4	8.5
Maximum score	6	5	12.5
		6	18.2

Table 9B. CHA$_2$DS$_2$-VASc Stroke Risk Score in AF

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stroke Rate, %
CHA$_2$DS$_2$-VASc			
Congestive heart failure	1	0	0
Hypertension	1	1	1.3
Age ≥ 75	2	2	2.2
Diabetes	1	3	3.2
Stroke/TIA/thromboembolism	2	4	4.0
Vascular disease	1	5	6.7
Age 65–74	1	6	9.8
Sex category (female)	1	7	9.6
Maximum score	9	8	6.7
		9	15.2

AF = atrial fibrillation; TIA = transient ischemic attack.

Information from: January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;23:2071-104.

b. Anticoagulation decisions should balance the risk of stroke versus the risks of bleeding in the context of duration of bridging and/or lack of anticoagulation. Scoring systems have been described to help assess bleeding risk in anticoagulation decisions for patients with AF on warfarin anticoagulation (Table 10). Not unlike stroke risk scoring systems, these scoring systems were not founded in the context of critically ill patients.

c. Direct-acting oral anticoagulants (DOACs) are recommended over warfarin for patients with AF (exclusions: moderate to severe mitral stenosis, mechanical heart valve) (Chest 2018;154:1121-201; J Am Coll Cardiol 2019;12:104-32).

d. For patients with AF who have a CHA$_2$DS$_2$-VASc score of 2 or greater (men) and 3 or greater (women) and who have end-stage chronic kidney disease (creatinine clearance [CrCl] less than 15 mL/minute/1.73 m^2) or are receiving dialysis, it may be reasonable to prescribe warfarin (INR 2.0–3.0) or apixaban (J Am Coll Cardiol 2019;12:104-32).

Table 10. HAS-BLED or HEMOR$_2$RHAGES Bleeding Risk Scores in AF

Risk Factor Assessment	Score	Total Patient Score	Bleeds/100 Patient-Yr of Warfarin
HAS-BLED			
Hypertension	1	0	1.13
Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
Stroke	1	2	1.88
Bleeding	1	3	3.74
Labile INRs	1	4	8.70
Elderly (> 65 yr)	1	5	12.5
Drugs or alcohol (1 point each)	1 or 2	6	0[a]
		Any score	1.56
HEMOR$_2$RHAGES			
Hepatic or renal disease	1	0	1.9
Ethanol abuse	1	1	2.5
Malignancy	1	2	5.3
Older age	1	3	8.4
Reduced platelet count or function	1	4	10.4
Rebleeding risk	2	≥ 5	12.3
Hypertension (uncontrolled)	1	Any score	4.9
Anemia	1		
Genetic factors	1		
Excessive fall risk	1		
Stroke	1		

[a] Scores > 5 were too rare to determine risk, but are likely > 10%. AF = atrial fibrillation.

e. In the critically ill patient, parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparin may be more favorable if the benefit of anticoagulation exceeds the risk of bleeding. Unfractionated heparin infusions would be favored more than low-molecular-weight heparin in renal failure (CrCl less than 30 mL/minute/1.73 m^2).

f. For anticoagulation of most critically ill patients, oral anticoagulation may be less favorable or even detrimental compared with parenteral anticoagulation.

i. Elimination of DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) is significantly affected in renal compromise. An additional consideration in the critical care setting is the feasibility of reversal in the event of an acute bleed or need for an invasive procedure. Novel antidotes continue to be studied and approved (idarucizumab, andexanet); however, clinical experience with reversibility in these settings is evolving. Finally, the aforementioned DOACs are not devoid of relevant drug-drug interactions, particularly when given in combination with strong CYP and/or P-glycoprotein inhibitors/inducers.

ii. Warfarin is challenging due to issues with malnutrition, drug interactions, and unpredictable dose response in the critically ill patient. Complications with this agent are more predictably managed than are complications with other oral anticoagulants if a patient requires an invasive procedure or develops an acute bleed, but warfarin use is still not without risk.

g. For patients with AF/flutter for 48 hours or more (or if undetermined) without therapeutic anticoagulation, absence of thrombus on the left side of the heart should be confirmed by transesophageal ECHO before pharmacologic or direct current cardioversion.

h. If AF/flutter for more than 48 hours or an unknown duration that requires direct current or pharmacologic cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated

i. For patients with AF/flutter taking anticoagulants who undergo cardiac stenting, the strongly recommended approach is to manage with dual therapy (anticoagulant + $P2Y_{12}$ inhibitor). Clopidogrel was the most widely studied $P2Y_{12}$ inhibitor in combination with anticoagulation (*J Am Coll Cardio*l. 2021;77(5):629-658; *N Engl J Med.* 2019;380(16):1509-1524). Direct oral anticoagulant medications have shown superior safety profiles to vitamin K antagonists in combination with $P2Y_{12}$ inhibitors. Guidance documents state that if triple antithrombotic therapy is to be used, it should be used for the shortest period possible for patients with a perceived high thrombotic risk. The guidance documents do not provide objective criteria for triple therapy use because they strongly favor dual therapy with an oral anticoagulant and $P2Y_{12}$ inhibitor. Dual therapy reduces the risk of bleeding compared with triple therapy without sacrificing ischemic efficacy. Further details surrounding recommendations are beyond the scope of this chapter but can be found in the 2023 ACC/AHA/ACCP/HRS Guideine for the Diagnosis and Management of Atrial Fibrillation Guidelines

Patient Case *(Continued)*

The appropriate intervention has been made from question 5, and the patient has not required any need for pacing. For the next 48 hours, J.M. continues on inotrope therapy and is being diuresed (his net fluid balance has been 1250 and 900 mL negative each day for the past 2 days). The transthoracic ECHO results showed J.M.'s ejection fraction to be 15%–20%, with a dilated, hypokinetic LV, severe mitral regurgitation, and dilated atria. No evidence of intracardiac thrombus was seen, but this could not be ruled out.

6. J.M. has had increasing premature atrial complexes on telemetry, and his heart rate has consistently been 83–96 beats/minute. He is receiving dobutamine at 5 mcg/kg/minute and a furosemide infusion at 10 mg/hour. The team is notified that J.M. has gone into AF with rapid ventricular response and a heart rate of 132 beats/minute (he has been in AF for about 30 minutes). His blood pressure is now 83/52 mm Hg. Which treatment plan would be most preferred for this patient?

   A. Synchronized cardioversion
   B. Metoprolol 5 mg intravenous push
   C. Adenosine 6 mg rapid intravenous push
   D. Amiodarone 300-mg intravenous push, followed by a continuous infusion at 1 mg/minute

7. J.M.'s BP and HR improved after the previous intervention; however, he remains in AF. The team is now concerned about evaluating the patient for anticoagulation. You are asked to provide input about the appropriateness of anticoagulation, given the patient's clinical course and past medical history. His calculated CHA_2DS_2-VASc score is 5 and HAS-BLED score is 5. The physician is considering anticoagulation with a heparin infusion while the patient is in the ICU and asks for a recommendation. Which is the most appropriate response?

   A. According to these scores, the patient's risk of bleeding is the same as his stroke risk; therefore, it would be reasonable to either initiate or withhold anticoagulation.
   B. According to these scores, the patient's risk of stroke exceeds his risk of bleeding; therefore, it would be reasonable to initiate heparin anticoagulation.
   C. The HAS-BLED score is less relevant because it is derived from chronic warfarin use. However, anticoagulation is still likely warranted eventually, given the patient's CHA_2DS_2-VASc score.
   D. The HAS-BLED and CHA_2DS_2-VASc scores are irrelevant to this patient's current care, and anticoagulation is not warranted.

VI. HEART FAILURE

A. Clinical Syndrome – Manifested because of congenital or acquired structural or functional myocardial dysfunction that impairs filling and/or emptying of the heart
   1. Mortality rate of 50% within 5 years of diagnosis
   2. Predominantly descriptive of LV and its pump performance and the ejection fraction
   3. Prognosis and treatment of HF largely depend on its etiology and staging.

Table 11. Diastolic Dysfunction Versus Systolic Dysfunction in HF

Type	Heart Failure with *Preserved* EF (HF*p*EF)	Heart Failure with *Reduced* EF (HF*r*EF)
Dysfunction	• Diastolic – blood filling the heart	• Systolic – blood emptying from the heart • May also coexist with impaired diastolic filling
Characteristics	• LVEF ≥ 50% • Impaired relaxation and filling of the ventricle before contraction • Commonly described as a “stiffened” ventricle • Contractility remains “normal”	• LVEF ≤ 40% • Impaired contraction and emptying of the ventricular cavity • Commonly described as a “dilated” ventricle
Clinical-management pearls	• Preload (volume optimization) is essential • As diastolic dysfunction worsens – ventricular preload and diastolic filling time must be maintained • Conditions acutely decreasing preload may lead to decompensation (e.g., tachyarrhythmias)	• Preload optimization essential – at high risk of volume overload • As systolic dysfunction worsens, cardiac output becomes increasingly afterload sensitive • Conditions acutely decreasing or increasing preload or increasing afterload may lead to decompensation • Volume overload and increasing myocardial dilation may contribute to decreased valvular coaptation and regurgitant flow
Common medications to avoid	• NSAIDs, with the exception of aspirin • Sympathomimetics	• NSAIDs, with the exception of aspirin • Sympathomimetics • Most antiarrhythmics except for amiodarone and dofetilide • Non-dihydropyridine calcium channel blockers

EF = ejection fraction; LVEF = left ventricular ejection fraction.

B. HF Etiologies
   1. Ischemic cardiomyopathy
      a. Accounts for about two-thirds of HF cases
      b. Caused by myocardial damage/death owing to CAD
   2. Non-ischemic cardiomyopathy
      a. Accounts for about one-third of HF cases
      b. May be attributed to other causes (Box 4)

Box 4. Non-ischemic Cardiomyopathies

Non-ischemic Cardiomyopathies

- Amyloidosis
- Sarcoidosis
- Drug induced
  - Alcohol
  - Anabolic steroids
  - Chemotherapy
    - Anthracyclines
    - Cyclophosphamide
    - Fluorouracil
    - Bevacizumab
    - Trastuzumab
    - Tyrosine kinase inhibitors
- Cocaine
- Methamphetamine
- Tricyclic antidepressants
- Anorexigens
- Familial
- Hypertension
- Hyper/hypothyroidism
- Hypertrophic obstructive (HOCM)
- Idiopathic
- Myocarditis
  - Autoimmune
  - Eosinophilic
  - Giant cell
  - Viral
  - Other infectious cause
- Non-compaction
- Peripartum
- Obesity
- Stress induced (Takotsubo)

C. RV Dysfunction and/or Failure (Exp Clin Cardiol 2013;18:27-30; J Am Coll Cardiol 2010;56:1435-46; Circ Heart Fail 2010;3:340-6; Anesth Analg 2009;108:422-33; Anesth Analg 2009;108:407-21)

1. Less well characterized than LV HF
2. No guidelines to direct management of acute RV failure
3. RV physiology
   a. The RV normally has only about one-sixth the myocardial mass of the LV. Primary means of compensation is heart rate increase.
   b. Normal RV ejection fraction is 40%–45%.
   c. Conduit to a low pressure system in the pulmonary vasculature (normally) and capable of accommodating for increased stroke volume but not able to compensate for acute pressure fluctuations.
   d. Physiologic deficits:
      i. Preload dependent
      ii. Interdependent on LV and septal contribution to contraction
      iii. Highly sensitive to acute increases in afterload. PVR elevations may be:
         (a) Drug induced (e.g., α_1 agents, protamine)
         (b) Caused by ventilator settings (high positive end-expiratory pressure [PEEP], high tidal volumes)
         (c) Caused by hypoxia
         (d) Caused by hypercarbia
         (e) Caused by pulmonary embolism
      iv. Poor elastic response to acute preload increases compared with LV
      v. Atypical geometric form contributes to:
         (a) Difficulty in objective assessment of RV function by ECHO
         (b) Increases susceptibility to further inefficiency/dysfunction when severely dilated

4. Etiologies of RV failure

Box 5. Etiologies of RV Failure (Exp Clin Cardiol 2013;18:27-30; J Am Coll Cardiol 2010;56:1435-46)

ARDS
Arrhythmias
Cardiac tamponade
Congenital heart disease
Heart transplantation (particularly if prolonged ischemic time)
Hypovolemia
Hypoxia
LV dysfunction
Mitral valve disease
Post-cardiac surgery
Pulmonary embolism
Pulmonary hypertension
Pulmonary regurgitation
Right coronary artery infarction/ischemia
RV overload
Sepsis
Tricuspid regurgitation/stenosis

D. Diagnostic Tests for New or Worsening HF – In addition to routine chemistry and CBC tests, additional testing may include:
   1. Liver function tests (may be indicative of congestive hepatopathy, if elevated)
   2. 12-lead ECG
   3. Troponin
   4. Left heart catheterization if suspected new ischemic contribution
   5. BNP or N-terminal pro-brain natriuretic peptide (elevations may help in the diagnosis of acutely decompensated HF in scenarios of uncertainty)
   6. Transthoracic or transesophageal ECHO
   7. Invasive hemodynamic monitoring (to guide volume optimization and dosing response to inotropes or vasopressors)
   8. For less common cardiomyopathies, noninvasive imaging (i.e., cardiac magnetic resonance imaging [MRI]) and/or myocardial biopsy may be required.

E. General Management Considerations
   1. Assess volume status.
      a. In selected cases of hypotension where HF is not known to be the exclusive culprit, small volume fluid challenges (250–500 mL intravenous fluid bolus) or passive leg raising (PLR) maneuvers may help show whether a patient is volume responsive.
      b. PLR is a reliable and alternative way of evaluating volume status, without the need to administer a fluid challenge (Curr Opin Crit Care 2017;23:237-43).
      c. Physical examination will generally guide fluid status decision.
         i. Jugular venous distension, hepatojugular reflux, lower extremity edema, rales on auscultation, dyspnea, paroxysmal nocturnal dyspnea
      d. Advanced hemodynamic parameters to suggest volume overload: pulmonary capillary wedge pressure greater than 18 mm Hg, pulmonary artery diastolic greater than 15 mm Hg, right atrial greater than 10 mm Hg

2. Once other causes of symptomatic congestion and/or low perfusion at rest have been ruled out and a diagnosis of decompensated HF is deemed likely, the following should be considered: If volume overloaded, provide intravenous diuretics at least equal to the patient's home oral dose (or alternatively up to 2–2.5 times the patient's home dose may be used) (*N Engl J Med*. 2011;364(9):797-805). For patients who are diuretic naive on admission, a starting dose of 20–80 mg of furosemide (or equivalent) is reasonable.
    a. Monitor for clinical improvement in symptoms and adequate urine output.
    b. Proactive evaluation of urine output adequacy should be used to facilitate optimization/escalation of diuretic regimen.
    c. Increase in loop diuretic dose and/or addition of sequential nephron blockade (i.e., metolazone) may be considered as needed to achieve the desired urine output and fluid balance. Recent evidence also suggests that SGLT2 inhibitors and acetazolamide may also help improve response to diuretic therapy (Circulation 2022;146:289-98; N Engl J Med 2022;387:1185-95). Administration of the loop diuretic as a continuous infusion can also be considered.
    d. For patients unresponsive to diuretic escalation as above or those with end-stage renal disease, hemodialysis and isolated ultrafiltration can be used for fluid removal.
3. Evaluate for use of vasodilator therapy.
    a. If normotensive or hypertensive (e.g., SBP greater than 100 mm Hg) in the presence of acute pulmonary edema (despite diuretic therapy):
        i. Continuous infusion intravenous vasodilators (e.g., nitroglycerin or nitroprusside) should be considered.
        ii. If the presence of high afterload is confirmed (systemic vascular resistance [SVR] greater than 1200 dynes/s/cm^5), then nitroprusside may be warranted more than other vasodilators. However, careful attention to patient selection is important because nitroprusside elimination is dependent on both hepatic metabolism and renal clearance. Note that nitroprusside is converted to nitric oxide and cyanide, with subsequent conversion to thiocyanate. Signs of potential toxicity include metabolic acidosis and mental status changes. In addition, patients receiving nitroprusside should have an arterial line for close blood pressure monitoring and typically a Swan-Ganz catheter in place.
        iii. Pulmonary vasodilators may be required in patients with evidence of pulmonary arterial hypertension: inhaled nitric oxide, epoprostenol, or alternatively phosphodiesterase type 5 inhibitors (sildenafil). Inhaled nitric oxide and epoprostenol may also be considered as short-term adjuncts in patients with right ventricular dysfunction and pulmonary hypertension in the perioperative setting. The delivery system and high cost associated with inhaled nitric oxide is a limitation relative to other options.
    b. If hypotensive (e.g., SBP of 100 mm Hg or less): Can consider vasodilators, but with caution
4. Monitor for clinical improvement of symptoms and adequate urine output.
    a. Proactive evaluation of urine output adequacy should be used to facilitate optimization/escalation of diuretic regimen. An optimized diuretic dose should produce 100–150 mL/hour of urine output at 6 hours or 50–70 mEq/L of urine sodium at 2 hours.
5. Evaluate for use of inotrope therapy
    a. If inadequate response on escalation of diuretics (and vasodilators, if appropriate), inotrope therapy should be considered, accounting for any concurrent physiologic considerations (e.g., right HF, pulmonary hypertension, ischemia, or valvular disease)

b. Dobutamine and milrinone are most often used for suspected or confirmed low cardiac output states. Milrinone may be preferred more than dobutamine in the presence of recent administration of β-blockade or in the setting of concomitant pulmonary hypertension (because of its post-β receptor effects and potent vasodilatory properties, respectively). In terms of pharmacokinetic differences, dobutamine has a faster onset and shorter half-life (2 min) compared with milrinone (half-life of 3 hrs with renal-dependent elimination). However, no differences in clinical efficacy or safety have been observed between agents. Both agents should be closely monitored for the development of proarrhythmias and worsening ischemia.

6. Evaluate for the appropriate initiation of GDMT
   a. Current guidelines recommend initiation of a 4-drug regimen for most patients with HFrEF as soon as possible, including in the inpatient setting. This 4-drug regimen is a combination of a RAAS inhibitor (angiotensin receptor/neprilysin inhibitor preferred), beta blocker, MRA, and sodium glucose co-transporter 2 inhibitor. For further guidance on GDMT indications, please consult current HF guidelines (Circulation 2022;145:e895-1032).
   b. Many providers discontinue β-blockers in acute decompensated HF, but this practice is generally not recommended because research indicates it can significantly increase the risk of in-hospital and short-term mortality, given the potential for increased sympathetic nervous system activation upon abrupt discontinuation. β-Blockers should be continued in patients with acute decompensated HF unless there are specific clinical reasons to discontinue them, like severe hemodynamic instability or evidence of shock (*Eur Heart J.* 2009;30(18):2186-2192).

VII. VALVULAR HEART DISEASE

A. Valvular heart disease is an important comorbid condition that must be considered in hemodynamic management of the critically ill patient. Valvular heart disease can also independently lead to the presenting critical illness.

B. Among the four cardiac valves, several etiologies[a] contribute to the manifested pathology; however, the depth and breadth of these etiologies are beyond the scope of this chapter. Nevertheless, conditions that may require repair/replacement include those listed in Table 12.

Table 12. Conditions That May Require Valvular Repair/Replacement

Stenosis	Narrowing at the opening of the valve(s) Can lead to concurrent regurgitation
Regurgitation	“Leaky” valve(s) resulting in less blood pumping forward through the heart
Prolapse	“Floppy” valve(s) with part of valve not working
Endocarditis	Infection of one or more valves
Malformation	Often occurs at birth when the valve (or valves) is defective

[a] Valvular disease secondary to rheumatic heart disease is a rare but possible contributor.

Table 13. Valvular Disease Characteristics and Management Considerations[a,b] (Circulation 2021;143:e72–227)

Valvular Disease Type	Management Considerations
Aortic stenosis (AS)	• One of the most common and serious valvular diseases seen in the ICU • As stenosis and disease progresses, severe/critical AS limits the heart to a fixed stroke volume; this inability to increase stroke volume occurs despite intrinsic or extrinsic attempts to compensate (i.e., increased chronotropy or inotropy) and often only increases myocardial oxygen demand without improving delivery • Must be extremely cautious in approaching and reacting to invasive hemodynamic variables (particularly cardiac output and cardiac index) – adding agents with inotropic/chronotropic effects may expedite demand ischemia and an acute MI because of the physiologic inability to increase cardiac output with a fixed partial LV outflow tract obstruction • For reasons similar to those previously listed, treating hypertension with afterload-reducing agents must be done judiciously because as afterload (SVR) decreases, cardiac output cannot increase • Can coexist with concurrent aortic insufficiency/regurgitation because the stenotic or calcified valve leaflets may no longer move and come together (coapt) well • These patients may be at risk of developing mitral regurgitation and subsequent increases in left atrial pressures (increasing risk of AF) because of increased LV filling pressures • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation • Patients need adequate preload; however, they can become symptomatic even with slight volume overload. As an example, atrial fibrillation can be very detrimental simply because it decreases preload to the ventricle • Patients with severe aortic stenosis and systolic HF (described as low output – low gradient) have a poorer prognosis
Aortic regurgitation (AR)	• Also known as aortic insufficiency (AI) • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation to maintain adequate cardiac output • Patients need adequate preload, but the predominant target is to maintain decreased afterload (SVR) to facilitate forward blood flow and cardiac output
Mitral stenosis (MS)	• Contributes to decreased LV filling and increased left atrial pressures; can increase risk of AF and secondary pulmonary hypertension • Increasing diastolic filling time and avoiding tachycardias can facilitate stabilization until valve is corrected • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures • Can coexist with concurrent mitral regurgitation because the stenotic or calcified valve leaflets may no longer move and coapt well
Mitral regurgitation (MR)	• Primary clinical target is to decrease LV afterload (SVR) to minimize augmentation of MR and to facilitate forward blood flow. If SVR is too high, blood will travel in the path of least resistance until an adequate LV pressure is generated to open the aortic valve (must exceed the systemic diastolic blood pressure) • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures

Table 13. Valvular Disease Characteristics and Management Considerations[a,b] (Circulation 2021;143:e72–227) *(continued)*

Valvular Disease Type	Management Considerations
Tricuspid regurgitation (TR)	• Likely to influence pulmonary artery catheter assessments of cardiac output by way of thermodilution technique • Can be influenced by infectious causes and presence of indwelling transvenous catheters or leads; but moderate or severe TR is more commonly a marker of RV overload and dysfunction

[a] Infective endocarditis can cause progressive valve disease, leading to regurgitant flow and impaired valve leaflet coaptation; however, it can also lead to near obstruction in some cases.

[b] Degree of valvular disease is graded as mild, moderate, or severe, as defined by objective ECHO or catheter-based assessments.

C. Procedural or Surgical Correction

Table 14. Procedural or Surgical Correction (Circulation 2017; Available at http://circ.ahajournals.org/content/early/2017/03/14/CIR.0000000000000503)

Balloon valvuloplasty	• Performed by percutaneous intervention as a temporizing intervention
Valve repair	• May entail direct surgical repair of a damaged valve leaflet or implantation of a ring at the valve annulus to facilitate improved coaptation of a regurgitant valve
Tissue (bioprosthetic) valve	• Made of animal or human tissue • Usually does not require long-term anticoagulation (see Table 15) • Does not last as long as a mechanical valve (may last 10–15 yr)
Mechanical valve	• Made of synthetic materials (newer valves use ceramic or carbon) • They are durable and generally unlikely to need replacement • Require lifelong anticoagulation • Warfarin is currently the only anticoagulant approved for use by the FDA in patients with mechanical heart valves (see Table 15)
Transcatheter aortic valve replacement (TAVR)	• Made of animal tissue (bioprosthetic) and attached to a wire frame stent and placed using catheter inside the old aortic valve • This may be considered in patients who are at higher perioperative risk for surgical aortic valve replacement or when surgery is not an option • Anticoagulation and/or antiplatelet agents are required for at least a short time after TAVR
Transcatheter edge-to-edge repair (TEER)	• Minimally invasive technique for treatment of symptomatic chronic moderate-severe or severe primary (degenerative) mitral regurgitation in patients at prohibitive surgical risk • A leaflet repair device (MitraClip) is currently the only FDA approved device for this indication • This device uses a cobalt chromium clip to suture the regurgitant orifices of the mitral valve leaflets together, thereby increasing coaptation • Anticoagulation and/or antiplatelet agents are required for at least a short time after TEER

D. Anticoagulation
  1. Three guidelines exist regarding valve anticoagulation, with varying agreement in the recommendations.
  2. Prosthetic mitral valves have increased risk of thrombosis (blood flow across the valve is passive and occurs during diastole) versus aortic valves, where blood flow across the valve is active occurring during systole.

Table 15. Summary of Anticoagulation Recommendations for Patients with Prosthetic Valves (Circulation 2017; Available at http://circ.ahajournals.org/content/early/2017/03/14/CIR.0000000000000503)

Procedure	Warfarin, Target INR Range	Class of Recommendation/ Level of Evidence[a]	Antiplatelet Therapy	Class of Recommendation/ Level of Evidence[a]
Mechanical AVR	2–3 (bileaflet or current-generation single-tilting disc and no risk factors for thromboembolism[b])	IB	Aspirin 81 mg daily may be considered if indicated for antiplatelet therapy and bleeding risk is low	IIb/B
	2.5–3.5 (older-generation [i.e., ball-in-cage valve, or with additional risk factors for thromboembolism[b]])	IB		
	For a mechanical On-X AVR and no thromboembolic risk factors, a goal INR of 1.5–2.0 may be reasonable starting ≥3 mo after surgery	IIb/B		
Bioprosthetic AVR	2–3 for ≥ 3 mo (and up to 6 mo if low bleed risk)	IIa/B	Aspirin 81 mg daily may be considered if indicated for antiplatelet and bleeding risk low	IIb/B

Table 15. Summary of Anticoagulation Recommendations for Patients with Prosthetic Valves (Circulation 2017; Available at http://circ.ahajournals.org/content/early/2017/03/14/CIR.0000000000000503) *(continued)*

Procedure	Warfarin, Target INR Range	Class of Recommendation/ Level of Evidence[a]	Antiplatelet Therapy	Class of Recommendation/ Level of Evidence[a]
Transcatheter AVR (TAVR)	2–3 for ≥ 3 mo if low bleed risk	IIb/B	Alternative to warfarin: Clopidogrel 75 mg daily for 6 mo and aspirin 81 mg daily. Although the above are guideline recommendations, the POPULAR-TAVI trial showed that aspirin monotherapy decreased the incidence of bleeding and the composite of bleeding and thromboembolic events compared with dual antiplatelet therapy for 3 mo (*N Engl J Med*. 2020;383(15):1447-1457)	IIb/B
Mechanical MVR	2.5–3.5	I/B	Aspirin 81 mg daily may be considered if indicated for antiplatelet therapy and bleeding risk is low	IIb/B
Bioprosthetic MVR	2–3 for ≥ 3 mo (and up to 6 mo if low bleed risk)	IIa/B	Aspirin 81 mg daily	IIa/B

[a] Atrial fibrillation, previous thromboembolism, left ventricular dysfunction, or hypercoagulable conditions.

[b] Class of Recommendations: I = evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; II = conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; IIa = weight of evidence/opinion is in favor of usefulness/efficacy; IIb = usefulness/efficacy is less well established by evidence/opinion; III = evidence of general agreement that the given treatment or procedure is not useful/effective and, in some cases, may be harmful; Levels of Evidence: A = data derived from several randomized clinical trials or meta-analyses; B = data derived from a single randomized trial or large nonrandomized studies; C = consensus of opinion of the experts and/or small studies, retrospective studies, registries.

[c] Target INR 2-3 for the first 3 mo.

E. Valve Thrombosis
   1. Highest risk within the first year after replacement
   2. Most predominant risk is in mechanical prosthetic valves, but can also occur with bioprosthetic valves
   3. Treatment involves systemic fibrinolytic treatment or surgical reoperation with varying success rates – Both carry significant risks of morbidity and mortality, including:
      a. Thrombolysis (predominantly recommended for right-sided valve thrombosis)
         i. Cardiac tamponade
         ii. Stroke/transient ischemic attack
         iii. Systemic embolization
         iv. Major bleeding
         v. Death
      b. Surgery (predominantly recommended for left-sided valve thrombosis)
         i. Cardiac tamponade
         ii. Stroke/transient ischemic attack
         iii. Renal failure
         iv. Heart block
         v. Systemic embolization
         vi. Prolonged ventilation
         vii. Major bleeding
         viii. Death

F. Other Cardiac Functional Defects
   1. Left ventricular outflow tract (LVOT) obstruction (Circulation 2020;142:e558-e631; Circulation 2008;117:429-39; J Am Coll Cardiol 2000;36:1344-54)
      a. Hypertrophic obstructive cardiomyopathy (HOCM)
         i. Genetic disease leading to hypertrophy of the LV (particularly the ventricular septum) with or without the presence of LV outflow tract obstruction
         ii. LVOT obstruction is of greatest concern when HOCM exists with systolic anterior motion (SAM) (see text that follows); however, in HOCM, LVOT obstruction can exist in the absence of SAM because of septal hypertrophy; nonetheless, acute clinical management is predominantly the same as outlined in 1.a.i–iii and in 1.b.i.
         iii. Treatment of HOCM without SAM relies heavily on the management of contributors to myocardial hypertrophy and diastolic HF.
            (a) Non-vasodilating β-blockers are first-line agents in the treatment of patients with HOCM and are commonly titrated to heart rate goals of 60–65 beats/minute.
            (b) Dihydropyridine calcium channel blockers (particularly verapamil) are recommended in patients with contraindications to β-blockade or in those without advanced HF or bradycardia.
            (c) For recommendations specific to HOCM (patients also with SAM), see “b” in the text that follows.
            (d) Patients with HOCM may be at increased risk of sudden cardiac death. Evaluation should consider the patient’s candidacy for implantable cardioverter-defibrillator placement by ambulatory ECG (Holter) monitoring at least biannually.
         iv. Treatment may be indicated by surgical septal myectomy or catheter-directed alcohol ablation.
      b. SAM of the mitral valve
         i. SAM and LVOT obstructions result in a systolic outflow tract obstruction and are commonly associated with HOCM but can also occur in other clinical scenarios, particularly after cardiac surgery.

ii. Can lead to severe cardiogenic shock
iii. SAM is more of a dynamic obstruction in which the degree of obstruction and flow gradient is dependent on heart rate, cardiac contractility, and ventricular preload volume.
    (a) In an underfilled LV, there is physically less distance between the mitral valve and septum, thus generating an increased risk of obstruction because the LVOT is generally narrower at the onset of systole, particularly if the mitral valve leaflet is affected.
    (b) Increasing cardiac contractility and heart rate increases LVOT obstruction and gradient by inducing a stronger contraction, increasing the contact between the septum and mitral leaflets, and increasing the rate of systolic attempts.
iv. For patients with SAM who have a potential for obstructive physiology, management involves maintaining normal or increased LV preload and low heart rates.
    (a) Acute hypotension is best managed with phenylephrine or vasopressin (pure vasoconstrictors) to selectively increase SVR without increasing contractility or heart rate. Concomitant β-blocker use may also be considered to improve cardiac filling.
    (b) Inotropes and vasopressors that mediate increases in heart rate or contractility should be avoided, if possible, because they may be harmful and worsen the LVOT.
    (c) Afterload-reducing agents (e.g., ACE inhibitors, ARBs, non-dihydropyridines) should be used with caution (if at all).

2. Septal defects (atrial or ventricular)
    a. Septal defects can be acquired (i.e., postinfarction ventricular septal defect) or can be congenital.
    b. Diagnosed predominantly by ECHO using a bubble study. If the patient presents in a seemingly low cardiac output state, a left-to-right intracardiac shunt should be suspected if Svo_2 saturations are greater than $Scvo_2$ saturations.
    c. Important principles
        i. Goals include minimizing the degree of intracardiac shunt while maintaining adequate cardiac output. It is generally favored to accept a right-to-left intracardiac shunt while recognizing that partial pressure of arterial oxygen ($Pao_{2)}$ saturations will be somewhat decreased and reflective of venous and arterial blood mixing in the LV before ejection.
        ii. Decreasing right-sided cardiac filling pressures can augment left-to-right intracardiac shunting of blood. Administration of venodilators (i.e., nitrates) or aggressive diuresis could augment left-to-right intracardiac shunts and lead to clinical deterioration.
        iii. Intravenous medications should preferably be filtered to minimize the risk of air/particulate embolus traveling through to the left side of the heart, being ejected, and causing a potential stroke.
    d. Treatment may include surgical correction or percutaneous catheter placement of a closure device.

VIII. ADVANCED THERAPIES FOR HEART FAILURE AND CARDIOGENIC SHOCK

A. The goals behind advanced therapies can be thought of as dynamic, depending on patient progression and resolution or presentation of comorbid conditions.

B. Dynamic Progression of HF Advanced Therapies

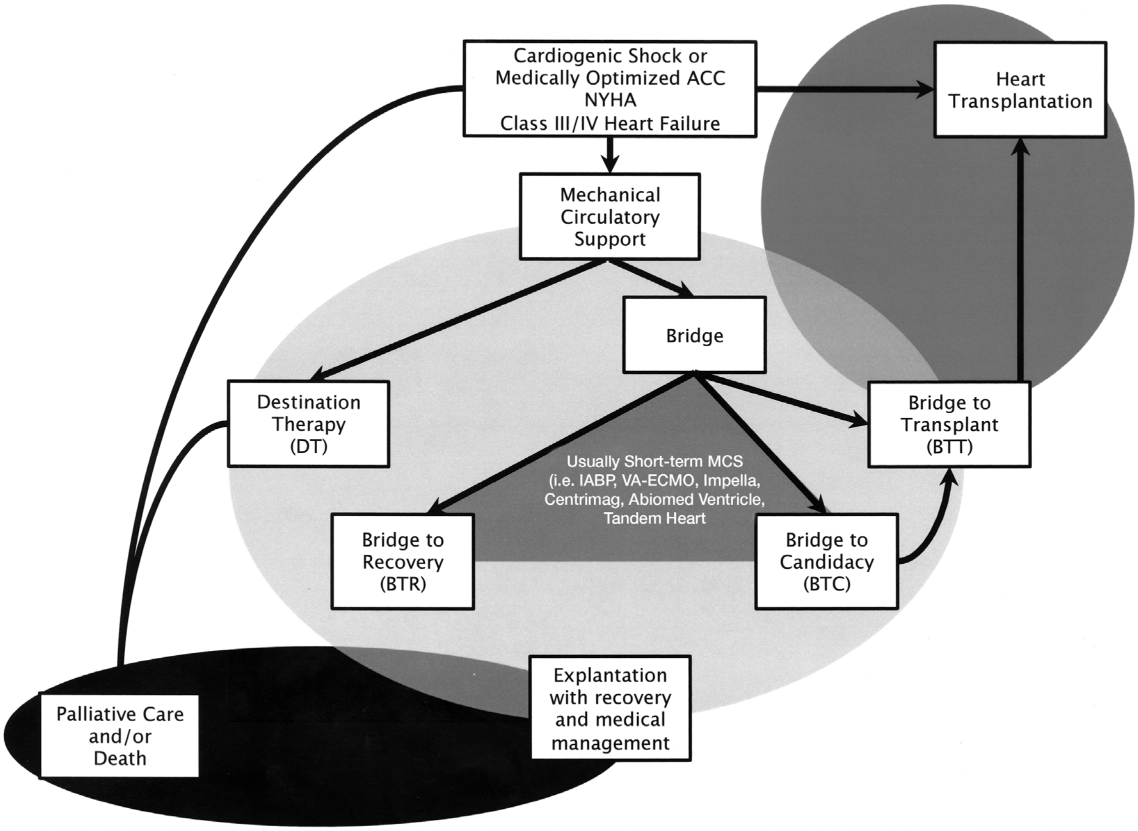

Cardiogenic Shock or Medically Optimized ACC NYHA Class III/IV Heart Failure
Heart Transplantation
Mechanical Circulatory Support
Bridge
Destination Therapy (DT)
Bridge to Transplant (BTT)
Usually Short-term MCS (i.e. IABP, VA-ECMO, Impella, Centrimag, Abiomed Ventricle, Tandem Heart
Bridge to Recovery (BTR)
Bridge to Candidacy (BTC)
Explantation with recovery and medical management
Palliative Care and/or Death

Figure 10. Dynamic progression of heart failure advanced therapies.

C. Mechanical Circulatory Support (MCS) (J Heart Lung Transplant 2013;32:157-87)
   1. Intent, duration, and type of MCS support depend on several factors, including patient acuity, comorbidities, and prognosis.
   2. Common terms
      a. Destination therapy – Formal designation for patients who meet the criteria for long-term mechanical support but who are not a transplant candidate because of relative or absolute contraindications
      b. Bridge to transplantation – Formal designation for patients eligible to be listed as candidates for heart transplantation
      c. Bridge to candidacy and bridge to recovery – Used in concept and are not formally recognized abbreviations but describe the approach to temporary MCS when short-term left ventricular assist devices (LVADs) are used to support a patient until a long-term prognosis can be determined, which may include explantation with recovery, implantation of long-term durable LVAD support, heart transplantation, or palliative care

Table 16. Mechanical Interventions for Shock

Short to Intermediate Term	
Intra-aortic balloon pump (IABP) counterpulsation	• Placed by femoral arterial catheter or percutaneously through the axillary artery and advanced up to the aorta • Inflation enables diastolic augmentation of systemic blood pressure to improve vital organ and coronary perfusion pressures • Deflation facilitates selective afterload during systole through a vacuum effect of the balloon deflation to ease cardiac output (does not technically increase cardiac output) • Can be set to trigger from ECG, pacer, or arterial line pressure, or can be manually set • Tachyarrhythmias and aortic regurgitation/insufficiency are not well supported with this means of MCS • Level of support coincides with timing of inflation/deflation per related heartbeat; for example: 1:1 = one inflation/deflation per every heartbeat (maximal support) 1:4 = one inflation/deflation for every fourth heartbeat (less support) • When setting duration in deflated state increases (providing less support), the thrombosis risk associated with the IABP increases, commonly requiring anticoagulation • Complications may include limb and visceral ischemia (distal pulses must be monitored three times a day), thrombocytopenia, hemolysis, balloon rupture.
Percutaneous VAD	• One common example is Impella: intraluminal axial support that provides varying degrees of LV output support (CP and 5.5) and RV output support (RP) • Another example is TandemHeart: left atrium-to-femoral artery bypass using transseptal cannulation • To date, only 1 trial has shown benefit in the management of post-MI congenital shock with temporary MCS (DANGER-SHOCK); all previous Impella and IABP have been negative (*N Engl J Med*. 2024;390(15):1382-1393) • May be considered in cardiogenic shock or as temporary support during high-risk PCI • Impella devices require a purge solution to run through the pump to prevent backflow of blood into the motor. This solution can be either heparin based or bicarbonate based. Sodium bicarbonate–based purge solution is an emerging alternative for patients with Impella devices who cannot receive heparin (*Pharmacotherapy*. 2021;41(11):932-942; *Ann Pharmacother*. 2023;57(6):646-652). Regardless of heparin or sodium bicarbonate, the base must always be mixed in dextrose 5% water. This purge solution should generally be used in combination with systemic anticoagulation • Anticoagulation regimen is a common topic of debate and medication safety discussion. In general, UFH is accepted as the standard anticoagulant for percutaneous VADs, and bivalirudin and argatroban can be used in patients with a history of or concern for HIT. • Complications may include hemolysis/bleeding, arrhythmias, and migration and/or malposition of the catheter/cannula
Extracorporeal or paracorporeal VAD	Examples include CentriMag, BVS 5000, and AB5000 ventricle

Table 16. Mechanical Interventions for Shock *(continued)*

Short to Intermediate Term	
Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO)	• Similar to cardiopulmonary bypass in which large-bore cannulas drain venous blood that is pumped through an oxygenator, where it is oxygenated and/or cleared of carbon dioxide and then actively pumped back into the body • Modality of support depends on the means of vascular cannulation ***Venoarterial:*** Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery in retrograde fashion up the aorta; potentially indicated for primary cardiogenic shock, cardiopulmonary failure, and post-cardiopulmonary circulatory shock ***Venovenous:*** Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery back to the right atrium; potentially indicated for hypoxic respiratory failure owing to any cause, hypercarbic respiratory failure with bronchospastic disease or other cause of carbon dioxide (CO_2) retention, or severe air leak syndromes
Long term	
Implantable LVADs	Examples include the HeartMate II (no longer commercially available), HVAD (no longer commercially available), and HeartMate 3
Total artificial heart	Example includes Syncardia TAH (biventricular support)

LVAD = left ventricular assist device; VAD = ventricular assist device.

- d. Anticoagulation considerations
  - i. Anticoagulation strategies are specific to the proprietary device, and many institutions have standardized protocols.
  - ii. Safety and efficacy of DOACs in patients with ventricular assist devices (VADs) have not been well established.

3. Complications of MCS (other than device failure)
   - a. Bleeding
     - i. Common sources
       - (a) Nasal/upper airway
       - (b) Gastrointestinal (GI)
       - (c) Arteriovenous malformations in one of the previously stated locations
       - (d) Hemolysis
     - ii. Workup and/or acute treatment options
       - (a) Laboratory workup
         - (1) Prothrombin time/INR/aPTT
         - (2) Increase frequency of hemoglobin/hematocrit evaluation.
         - (3) Multimeric von Willebrand testing for acquired von Willebrand factor deficiency (some clinicians believe that all patients with prolonged continuous flow MCS develop acquired von Willebrand disease)
         - (4) If no overt sign of bleeding – Consider hemolysis workup.
       - (b) If suspected/confirmed bleeding, hold anticoagulation and consider reversal with caution. Consider any history of bleeding/clotting-related problems and indications for antithrombotic therapy in addition to MCS.
       - (c) Obtain appropriate consults, and consider common interventions.
       - (d) Ear, nose, and throat:
         - (1) Evaluate for source control and/or cauterization.

(2) Mupirocin 2% (Bactroban) every 12 hours to each nostril to maintain moist nasal passages

(3) Oxymetazoline 0.05% (Afrin) to each nostril every 12 hours as needed for epistaxis

(e) Gastroenterology

(1) Intravenous proton pump inhibitor until location of GI source identified or for up to 72 hours. Intermittent intravenous dosing may also be considered.

(2) Enteroscopy with or without colonoscopy; may consider one or more of the following:

- Angiography and cautery
- Balloon-assisted enteroscopy
- Video-capsule enteroscopy
- Surgery

iii. Long-term management

(a) Consider decreasing anticoagulation/antiplatelet therapy intensity.

(b) Refractory bleeding despite previously stated interventions

(1) Consider role of oral antifibrinolytics (i.e., aminocaproic acid).

(2) Consider role of desmopressin or von Willebrand factor replacement if confirmed acquired von Willebrand disease and if LVAD speed cannot be further decreased.

(3) If GI arteriovenous malformations are present that are not amenable to intervention, octreotide 50 mcg subcutaneously every 8 hours may be considered.

b. Intravenous proton pump inhibitor

i. Hemolysis may be the presenting symptom of an underlying process, including infection, pump thrombosis, or other mechanical or physiologic dysfunction.

ii. Common presentation includes:

(a) Nonhemorrhagic anemia

(b) Urine color changes with appearance of hematuria; in severe cases, can be brown or black

(c) Hyperkalemia

(d) LVAD pump alarms

iii. Workup for contributing factors:

(a) Evaluate LVAD and cardiac function for contributing factors, including documentation and alarm history for suction events, power spikes, speed changes, volume status, RV function, arrhythmias

(1) Evaluate cannula(e) position and evaluate for obstruction/thrombus by ECHO or computed tomography (CT).

(2) Evaluate RV function by ECHO.

(3) Evaluate for intra-device thrombosis by ECHO ramp testing (Echocardiography 2014;31:E5-9; J Am Coll Cardiol 2013;62:2149-50; J Am Coll Cardiol 2012;60:1764-75).

(b) Ensure adherence to anticoagulation regimen according to patient's established goals.

(c) Evaluate laboratory values to establish the presence and degree of hemolysis and to identify any other potential contributors.

(1) Lactate dehydrogenase (LDH); normal values are 300–600 IU/L for most forms of MCS.

(2) Haptoglobin

(3) Plasma-free hemoglobin

(4) Blood cultures (an association has been identified with bacteremia and hemolysis in patients with LVADs – in some cases, presenting as thrombosis).

(5) Urine assessment – Send baseline urinalysis, urine culture, and appearance of changes daily to assess for improvement. Likely hemolysis, as evidenced by the presence of casts and color changes (darkened tea, red, or black are highly suggestive of hemolysis).

        - (d) Other laboratory values/considerations
            - (1) Hypercoagulable states (i.e., heparin-induced thrombocytopenia [HIT])
            - (2) CBC with differential
            - (3) Reticulocyte count
    - iv. Treatment
        - (a) Address any evidence of mechanical dysfunction by adjusting speed/flow rates, if possible.
        - (b) Consider medical optimization of RV function.
        - (c) If hypovolemic, give volume challenge. Consider alkalinization of urine and optimize fluid status (sodium bicarbonate 150 mEq/1000 mL of sterile water) at 0.5–1 mL/kg/hour; treat to a goal urine pH of greater than 7.5 to avoid additional hemolysis/hemoglobinuria-related acute kidney injury.
        - (d) Evaluate and optimize anticoagulation strategy.
            - (1) Ensure therapeutic anticoagulation with heparin or warfarin.
            - (2) Antithrombotic therapy that is more aggressive may be appropriate. Optimal acute antithrombotic strategies, although not yet defined, may include heparin infusion, glycoprotein IIb/IIIa infusions, parenteral direct thrombin inhibitors, or thrombolytics.
            - (3) Severe hemolysis can potentiate platelet activation – Can consider glycoprotein IIb/IIIa antagonist therapy (see Table 5), depending on bleeding risks and potential surgical plan.
        - (e) Reassess long-term antithrombotic strategy.
            - (1) Consider augmentation of antiplatelet therapy, or increase the INR therapeutic goal range.
            - (2) If thought to be related to a concurrent infection, can consider acutely increasing anticoagulation goals until infection control is gained
- c. Infection
    - i. LVAD infections are often complex and have been characterized by the International Society for Heart & Lung Transplantation in the following manner (*J Heart Lung Transplant.* 2020;39(4):S487):
        - (a) VAD-specific infections
            - (1) Pump and/or cannula infections
            - (2) Pocket infections
            - (3) Percutaneous driveline infections
                - Superficial infection
                - Deep infection
        - (b) VAD-related infections
            - (1) Infective endocarditis
            - (2) Bloodstream infections that may be VAD related or non–VAD related
            - (3) Mediastinitis
                - Sternal wound infection: Surgical site infection-organ space
                - VAD pocket infection (continuous with mediastinum or already situated in the mediastinum, depending on the device used)
                - Other causes of mediastinitis, perforation of the esophagus
            - (4) Non-VAD infections
                - Lower respiratory tract infection
                - Cholecystitis
                - *Clostridium difficile* infection
                - Urinary tract infection

- ii. Antibiotic treatment
  - (a) Antibiotic coverage should account for site of suspected infection, previous pathogens and susceptibilities, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. Prophylactic antibiotic coverage for VAD-related or non–VAD-related surgical procedures should account for site of procedure, previous infections, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. In some circumstances, this requires broader prophylactic antibiotic coverage (Interact Cardiovasc Thorac Surg 2012;14:209-14).
  - (b) Treatment duration depends largely on the type of infection. However, if the infection is VAD related or VAD specific, prolonged antimicrobial therapy (more than 4 weeks) is commonly used.
  - (c) Because LVAD exchange is not without considerable risk, long-term oral antibiotic suppression therapy may be considered for some infections.

Patient Case *(Continued)*

8. J.M. is no longer in AF but remains in cardiogenic shock. The cardiac intensive care unit team has consulted the cardiothoracic surgeons for evaluation of his mitral valve disease and has considered advanced HF therapies. In the patient's decompensated state, he would likely need additional optimization if he were to undergo surgery. Which temporary means of mechanical circulatory support (MCS) might be most favorable to help stabilize this patient's cardiogenic shock in the setting of moderate to severe mitral regurgitation?
   - A. Venoarterial extracorporeal membrane oxygenation (ECMO)
   - B. Venovenous ECMO
   - C. Intra-aortic balloon counterpulsation
   - D. None; the patient likely requires urgent surgery.

D. Heart Transplantation (*J Heart Lung Transplant.* 2024;43(10):1529-1628.e54)

1. Transplantation remains the gold-standard treatment for end-stage HF.
2. Many variables limit the utility of heart transplantation, foremost of which is donor availability and donor-recipient tissue compatibility.
3. Other limitations may include recipient characteristics of:
   - a. Mental health
   - b. Social support
   - c. Adherence to medication and appointments
   - d. Severe pulmonary hypertension
   - e. Cancer
   - f. Infection
   - g. Tobacco or ethanol use
   - h. Illicit drug use
4. Additional considerations associated with thoracic transplantation in the ICU, such as immunosuppression, rejection, and other complications, are beyond the scope of this review.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

Given this patient's CAD, type 2 diabetes, dyslipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy, only Answer B consists of the three agents that reduce morbidity and mortality among these comorbidities: carvedilol (HF and potentially diabetes), spironolactone (HF progression post-MI), and lisinopril (HF and diabetes), making Answer B correct and Answers A (Amlodipine, clopidogrel, and sitagliptin.), C (Pravastatin, amlodipine, and aspirin 325 mg), and D (Prasugrel, sildenafil, and atenolol) incorrect.

2. **Answer: C**

Although many of these tests might be helpful in this patient's differential diagnosis, the most likely consideration would be respiratory decompensation or an HF decompensation, given the patient's presentation; thus, a chest radiograph, ECHO, BNP, and lactate would be most appropriate, making Answer C correct. Answer A is incorrect; although an infectious etiology cannot be ruled out, it is less likely than noninfectious cardiorespiratory differentials. Answer B is not the best answer; although serial troponins and an ABG could be argued for, liver function tests are unlikely to provide additional insight into this patient's differential. Answer D also is not the best answer; although it provides additional information for hemodynamic assessment, it is lacking in an assessment of cardiac function, which is a likely contributor to the patient's presentation.

3. **Answer: D**

Dobutamine would be the ideal choice, given the patient's acutely worsening cardiac index and malperfusion and its rapid onset; this would facilitate β_2 arterial vasodilation (both SVR and PVR reduction) as well as increase chronotropy and inotropy. Milrinone, although likely beneficial for both cardiac index and PVR reduction, would be less favorable, given that its time to peak effect will exceed 6 hours (the time required to achieve greater than 87.5% of steady state, even in normal renal function), and the dosing is rather high for safe initiation of therapy. Neither norepinephrine nor epinephrine would be favored (particularly at these doses) because the patient's MAP is currently elevated, and these agents would contribute to increased α_1-mediated afterload increases, causing increased myocardial workload in a patient who already has decompensated systolic HF. Answer D (dobutamine 5 mcg/kg/min) is correct, and Answers A (norepinephrine 0.08 mcg/kg/min), B (epinephrine 0.08 mcg/kg/min), and C (Milrinone 0.75 mcg/kg/min) are incorrect.

4. **Answer: D**

The patient's troponin elevation is most likely a result of the patient's decompensated HF (especially considering clinical evidence of acute HF, such as high BNP, CVP, and low cardiac output) superimposed on chronic CAD (Answer D is correct). Given the patient's chemistry and ABG results, chronic obstructive pulmonary disease (Answer B) is highly unlikely. Although this presentation could be attributed to NSTEMI (Answer A), it is less likely, given the lack of new ST-T changes on ECG and the accompanying evidence of an HF exacerbation. Sepsis (Answer C) is also a potential contributor to troponin elevation; by comparison, an infectious etiology is less likely in this patient's case.

5. **Answer: A**

Ticagrelor has been associated with adenosine-mediated dyspnea and bradycardia; therefore, this medication should be evaluated as a contributing cause. According to the current ACC/AHA guidelines, this patient should continue $P2Y_{12}$ inhibitor therapy because his stent was placed less than 12 months ago, and he should continue aspirin therapy indefinitely (Answer A is correct). Conversely, it would not be appropriate to stop ticagrelor without switching to an alternative $P2Y_{12}$ inhibitor (Answer B is incorrect). A likely cause has been identified (Answer C is incorrect), and the patient has no evidence of hyperkalemia (Answer D is incorrect).

6. **Answer: A**

Because of this patient's hypotension and ongoing cardiogenic shock, synchronized cardioversion would be preferred (Answer A is correct). Metoprolol (Answer B) would be unfavorable because of the patient's concurrent dobutamine use and hypotension; similarly, amiodarone 300 mg intravenous push (Answer D) could contribute to further hypotension. The primary of role of adenosine (Answer C) is to slow AV nodal conduction when patients are tachycardiac with a regular rhythm (i.e., supraventricular tachycardia) to terminate the arrhythmia or to help differentiate atrial from ventricular arrhythmias.

7. **Answer: C**

The physician is considering heparin anticoagulation while the patient is in the ICU. Although valuable to consider for long-term anticoagulation, the HAS-BLED score is not validated for bleeding risk specific to heparin anticoagulation. Nonetheless, given the patient's CHA_2DS_2-VASc score (annual stroke risk of 6.7%), anticoagulation should be considered, making Answer C correct and Answer D ("anticoagulation is not warranted") incorrect. Answer A, "the patient's risk of bleeding is the same as his stroke risk," and Answer B, "the patient's risk of stroke exceeds his risk of bleeding," are incorrect statements because the foundation of these scores does not include risk of thromboembolism during ICU stay, nor do the scores assess risk of bleeding on heparin infusions.

8. **Answer: C**

Given his ongoing cardiogenic shock, this patient is unlikely to remain stable without intervention; thus, Answer D is incorrect. To help stabilize him, intra-aortic balloon counterpulsation (Answer C) would best facilitate selective afterload reduction during systole (increasing cardiac output in a patient with a low ejection fraction and severe mitral regurgitation) while providing augmented diastolic pressures. Venovenous ECMO (Answer B) is unlikely to help because this means of MCS depends on a functional LV and RV to provide forward blood flow. Venoarterial ECMO (Answer A) may stabilize the patient; however, it would increase afterload on the aortic valve, which could worsen his mitral regurgitation. Furthermore, this degree of MCS may be unwarranted at this time unless the patient develops progressive hypoxic cardiopulmonary failure.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

A diagnosis of cardiogenic shock is most likely, given the patient's history, presentation, ongoing vasopressor requirement, elevated BNP, and lack of infectious symptoms (Answer A is incorrect). Furthermore, this patient has positive troponins and ST-segment elevation in leads II, III, and aVF (inferior leads), making STEMI the primary diagnosis and reason for cardiogenic shock (Answer C is correct; Answer D is incorrect). The presence of hypotension and bradycardia are more likely consistent with complications of an inferior MI with possible RV involvement, as opposed to an acute exacerbation of HF. The patient also has a preserved LVEF and not systolic HF (Answer B is incorrect).

2. **Answer: D**

ST-segment elevation in leads II, III, and aVF (inferior) are most consistent with the right coronary artery (Answer D is correct). Answers A (left main coronary artery), B (left anterior descending artery), and C (left circumflex coronary artery) are incorrect.

3. **Answer: B**

According to the SOAP II investigation, dopamine is associated with increased rates of adverse events in patients with cardiogenic shock compared with norepinephrine (Answer B is correct; Answer A is incorrect). Milrinone (Answer C), although helpful in some patients with HF, would not be favored, given the patient's current hypotension and acute renal failure. Normal saline administration (Answer D) would likely be detrimental because of the patient's signs of fluid overload, including BNP elevation, hyponatremia, and rales on examination.

4. **Answer: A**

Lidocaine would be most favorable in patients with ischemia-mediated ventricular arrhythmias, and although the patient is not currently in VT, he is having persistent premature ventricular contractions (bigeminy), further increasing concern for ongoing ischemia and myocardial irritability (Answer A is correct). Metoprolol (Answer C) and diltiazem (Answer D) would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Amiodarone 300 mg intravenous push (Answer B) is no longer appropriate because the patient has a pulse and blood pressure and is currently not in VT. Furthermore, rapid administration of amiodarone may lead to worsening hypotension.

5. **Answer: A**

The patient's heart catheterization was performed through the femoral artery, a vessel that is much more difficult to compress to facilitate hemostasis. Hematomas can occur at the access site; however, the most serious bleeding complication associated with this access site is a retroperitoneal bleed (Answer A is correct). Answer B (dissection/rupture), Answer C (stent thrombosis), and Answer D (papillary muscle rupture) are incorrect.

6. **Answer: C**

Vasopressin would be favored because, when administered at normal physiologic doses, it mediates predominant increases in SVR while minimally affecting the PVR (Answer C is correct). Phenylephrine (Answer B), however, will increase both PVR and SVR by the α_1-receptors. Given the patient's ongoing hypotension, low cardiac index, and rising CVP, inaction (Answer A) would be inappropriate, and additional volume administration (Answer D) would be detrimental in the setting of volume overload and RV failure.

7. **Answer: B**

Amiodarone boluses would be safest if administered slowly for 10 minutes to avoid additional hypotension, followed by a continuous infusion (Answer B is correct; Answer A is incorrect). Metoprolol (Answer C) and diltiazem (Answer D) would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements.

8. **Answer: D**

Because of the diagnosis of acute MI, current quality measures would require initiation of or documentation to contraindications for each item except for ACE inhibitors/ARBs (Answer D) because the patient still has an LVEF greater than 40%. Answer A (aspirin contraindication), Answer B (statin contraindication), and C (β-blocker contraindication) are incorrect.

APPENDIX A – OVERVIEW OF ANTI-ARRHYTHMICS

Class	MOA	Drug (available dosage forms)	ECG Effects			Management Considerations and Pearls	Notable Drug Interactions	Defibril-lation Threshold	TdP risk (%)
			PR	QRS	QT/QTc				
IA	Sodium channel blockade (inter-mediate potency)	Quinidine (PO and IV)	↑↓	↑	↑	Different formulations available (no exact conversions) α-Blockade may contribute to hypotension Prolonged half-life in CHF and hepatic dysfunction May require dose adjustments in renal and/or hepatic dysfunction Enhanced AV node conduction usually requires combination with AV node-blocking agent	CYP2D6 (inhibitor) CYP3A4 (substrate and inhibitor) QT-prolonging drugs	↑	2–8
		Procainamide (IV)	↑	↑	↑	May contribute to hypotension Metabolized by hepatic acetylation Active metabolite (NAPA) renally eliminated and has increased class III properties Dialyzable	QT-prolonging drugs	↑↓	1–10
		Disopyramide (PO)	↑↓	↑	↑	May require dose adjustments in renal and/or hepatic dysfunction Potent anticholinergic adverse effects May be used to treat hypertrophic cardiomyopathy	CYP3A4 (substrate) QT-prolonging drugs	↑	1–3
IB	Sodium channel blockade (low potency)	Lidocaine (IV)	N/A	N/A	N/A or ↓	Ventricular arrhythmias only Increased risk of toxicities in hepatic dysfunction, CHF, and elderly patients Enhanced efficacy in ischemic tissue Adverse effects include CNS depression, somnolence, tremors, seizures Lidocaine concentrations may be checked (total: 1.5-5 mcg/mL; free: 0.5-2 mcg/mL)	CYP3A4 (substrate)	↑	
		Mexiletine (PO)				Ventricular arrhythmias only Prolonged half-life in CHF and hepatic dysfunction Oral derivative of lidocaine	CYP2D6 (substrate) CYP1A2	↑	
IC	Sodium channel blockade (high potency)	Flecainide (PO)	↑	↑	N/A or ↑	Useful for AF/flutter in patients without structural heart disease Increased risk of mortality post-MI (Cardiac Arrhythmia Suppression Trial [CAST]) Avoid in CHF because of its potent negative inotropic effects Combine with AV node blocker to prevent rapid atrial flutter	CYP2D6	↑	
		Propafenone (PO)				Useful for AF/flutter in patients without structural heart disease Increased risk of mortality post-MI (CAST trial) Avoid in CHF because of its potent negative inotropic effects Combine with AV node blocker to prevent rapid atrial flutter SR and IR formulations not equivalent	First-pass metabolism CYP2D6, CYP3A4, CYP1A2 substrate	↑↓	

APPENDIX A – OVERVIEW OF ANTI-ARRHYTHMICS *(continued)*

II	β-Blockade	Ex. Carvedilol (PO) Labetalol (PO/IV) Metoprolol (PO/IV) Esmolol (IV)	N/A or ↑	N/A	N/A or ↓	Sinus bradycardia AV block Hypotension more likely with nonselective agents Continuous infusions of esmolol or labetalol may contribute to large amounts of fluid	Predominantly CYP2D6	N/A	
III	Potassium channel blockade	Dofetilide (PO)	N/A or ↑	N/A or ↑	↑	Requires ECG monitoring for initiation, dose titration, reinitiation, or introduction of new interacting agents Requires renal dosing adjustments Mg and K monitoring Circulation 2024;149:e1–156.	CYP3A4 Trimethoprim, verapamil, HCTZ, and many others contraindicated QT-prolonging drugs	↓	1–8
		Ibutilide (IV)				Only indicated for cardioversion of AF or enhancement of electrical cardioversion	QT-prolonging drugs	↓	1–8
		Sotalol (PO/IV)				Requires renal dosing adjustments Bradycardia Mg and K monitoring Circulation 2024;149:e1–156.	QT-prolonging drugs	↓	1–6
		Amiodarone (PO/IV)				Multi–channel-blocking properties Monitor liver, thyroid, and pulmonary function tests Average half-life 53 days; highly lipophilic; active metabolite Bradycardia and hypotension High protein binding	Inhibits CYP3A4, CYP2D6, CYP2C9 Adjust warfarin and digoxin by 50%	↑	< 1
		Dronedarone (PO)				Multi–channel-blocking properties Only approved for AF/flutter; less efficacious vs. amiodarone Less potential for organ-system toxicity vs. amiodarone Avoid in CHF, particularly NYHA class III/IV Bradycardia Liver function tests within first 6 mo of therapy	Inhibits CYP3A4, CYP2D6, CYP2C9		< 1
IV	Calcium channel blockade	Verapamil (PO/IV)	↑	N/A	N/A	Hepatic dosing Sinus bradycardia Negative inotrope – avoid in patients with systolic heart failure	CYP3A4 (substrate and inhibitor)	N/A	
		Diltiazem (PO/IV)				Decreased dosing in elderly patients and patients with hepatic dysfunction Bradycardia Negative inotrope - avoid in patients with systolic heart failure	CYP3A4 (substrate and inhibitor)	N/A	
Misc.	Others	Digoxin (PO/IV)	↑	N/A	N/A	Alternative for rate control of AF/flutter; also used for systolic heart failure Decreased dosing in elderly and patients with kidney dysfunction Loading dose may be given based on ideal body weight Not dialyzable Digoxin concentrations may be checked (AF/flutter: 0.8-2 ng/mL; heart failure: 0.5-0.9 ng/mL)	Many interactions		
		Adenosine (IV)	↑			Half-life < 10 s Used for acute treatment of AV node reentrant tachycardias Can help to distinguish atrial from ventricular arrhythmias			
		Magnesium (IV)	↑			Used to treat Torsades and arrhythmias associated with hypomagnesemia Adjunctive treatment for atrial fibrillation with rapid ventricular response to slow ventricular rate. Given with AV nodal blocking agent			

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; CNS = central nervous system; ECG = electrocardiogram; HCTZ = hydrochlorothiazide; IR = immediate release; IV = intravenous(ly); MI = myocardial infarction; MOA = mechanism of action; NAPA = N-acetylprocainamide; N/A = not applicable; NYHA = New York Heart Association; PO = oral(ly); SR = sustained release; TdP = Torsades de pointes.

CARDIOVASCULAR CRITICAL CARE II

PATRICK M. WIERUSZEWSKI, PHARM.D., BCCCP, FCCM

MAYO CLINIC COLLEGE OF MEDICINE
MAYO CLINIC
ROCHESTER, MINNESOTA

Cardiovascular Critical Care II

Patrick M. Wieruszewski, Pharm.D., BCCCP, FCCM

Mayo Clinic College of Medicine
Mayo Clinic
Rochester, Minnesota

Learning Objectives

1. Manage cardiac arrest from the initiation of basic life support to the use of post–cardiac arrest care.
2. List the indications and special considerations for medication administration during cardiac arrest.
3. Categorize the patient groups that should receive temperature control after cardiac arrest.
4. Develop treatment plans for common complications of temperature control after cardiac arrest.
5. Analyze the therapeutic goals and clinical indications for the medications used in hypertensive emergency.

Abbreviations in This Chapter

ACLS	Advanced cardiac life support
AED	Automated external defibrillator
BLS	Basic life support
BPV	Blood pressure variability
CPR	Cardiopulmonary resuscitation
DBP	Diastolic blood pressure
ED	Emergency department
ICP	Intracranial pressure
ICU	Intensive care unit
IO	Intraosseous
MAP	Mean arterial pressure
MICU	Medical intensive care unit
PEA	Pulseless electrical activity
pVT	Pulseless ventricular tachycardia
ROSC	Return of spontaneous circulation
SCA	Sudden cardiac arrest
SBP	Systolic blood pressure
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–5 pertain to the following case.

T.B. is a 72-year-old man with a history of atrial fibrillation, coronary artery disease with drug-eluting stent placement in 2009, heart failure with reduced ejection fraction (most recent ejection fraction was 45% on echocardiogram in 2018), and gastroesophageal reflux disease. T.B. is sent to the catheterization laboratory for suspected acute myocardial infarction. Laboratory values for T.B. are as follows: international normalized ratio (INR) 1, platelet count 200,000/mm^3, hemoglobin 12 g/dL, serum creatinine (SCr) 1.7 mg/dL (baseline 1.5 mg/dL), white blood cell count (WBC) 17 x 10^3 cells/mm^3, and aspartate aminotransferase (AST) 100 IU/L. He is admitted to the coronary care unit for observation after catheterization when he suddenly loses consciousness and becomes pulseless. The coronary care unit team of which you are part is called to the bedside. Of note, T.B. has peripheral intravenous access, and before this event, was on room air without any oxygen support.

1. Which is the most appropriate first step in T.B.'s resuscitation?
   A. Promptly intubate because this is likely a hypoxic pulmonary arrest.
   B. Place central line for vasopressor administration.
   C. Provide chest compressions.
   D. Give 2 breaths by bag-mask ventilator.

2. The monitor reveals that T.B. is in ventricular fibrillation (VF), and he remains pulseless. Which is the most appropriate management of T.B.'s VF arrest?
   A. Provide an unsynchronized shock/defibrillation at 120 J from a biphasic defibrillator.
   B. Give intravenous amiodarone at a dose of 300 mg.
   C. Give intravenous atropine at a dose of 1 mg.
   D. Provide emergency transcutaneous pacing.

3. T.B.'s rhythm changes from VF to pulseless electrical activity (PEA) on the monitor. Which is the most appropriate management of T.B.'s PEA arrest?
   A. Provide an unsynchronized shock/defibrillation at 120 J from a biphasic defibrillator.
   B. Chest compressions while considering treatable causes of cardiac arrest.
   C. Give intravenous lidocaine 1 mg/kg x 1, followed by an infusion at 1 mg/minute.
   D. Give intravenous atropine at a dose of 1 mg.

4. T.B. has return of spontaneous circulation (ROSC) after 15 minutes of total resuscitation. The team is deciding whether temperature control would be appropriate for T.B. Which is the most accurate statement regarding temperature control for T.B.?
   A. He should not be considered because his initial presentation was VF arrest.
   B. He should not be considered because he has transaminitis.
   C. He should be considered with SCr monitoring.
   D. He should be considered, but thrombolysis should be initiated concurrently because of the associated risk of clotting.

5. The medical team wants further information about the literature regarding temperature control. Which is the most appropriate information regarding the data to support temperature control?
   A. Improves survival in PEA cardiac arrests.
   B. Shown to improve neurologic outcomes.
   C. Superiority found when targeting a core temperature of 36°C compared with 33°C.
   D. Most studied in patients with asystole.

Questions 6–8 pertain to the following case.
J.H. is a 48-year-old woman with no known medical history who presents to the emergency department (ED) for acute onset of shortness of breath, right-side pain, and some blurry vision. She denies any illicit drug or cigarette use, but she confirms social alcohol intake (about 3 drinks per week). Urine toxicology is negative. Initial vital signs are as follows: blood pressure (BP) 202/140 mm Hg, heart rate (HR) 88 beats/minute, respiratory rate (RR) 22 breaths/minute, and pain 4/10 (chest and right-side pain). Initial laboratory values are as follows: SCr 0.8 mg/dL, AST 608 U/L, ALT 458 U/L, lipase 20 U/L, total bilirubin (Tbil) 1 mg/dL, direct bilirubin (Dbil) 0.4 mg/dL, WBC 6 x 10^3 cells/mm^3, hemoglobin 11 mg/dL, troponin T less than 0.01 ng/mL, and D-dimer less than 0.5 mcg/mL. Chest radiography shows moderate bilateral pleural effusions and no focal consolidations. Chest computed tomography (CT) is negative for pulmonary embolism. Of note, J.H. is taking no prescription or over-the-counter medications.

6. Which laboratory abnormality or presenting symptom best qualifies J.H. for hypertensive emergency?
   A. None; she is having asymptomatic markedly elevated blood pressure.
   B. Her SCr.
   C. Her AST/ALT.
   D. Her D-dimer.

7. Which is the most appropriate initial treatment strategy for J.H.'s BP?
   A. Phentolamine 1 mg intravenously every 30 minutes.
   B. Metoprolol 25 mg orally every 12 hours.
   C. Nitroprusside 0.25 mcg/kg/minute by continuous intravenous infusion.
   D. Enalaprilat 10 mg intravenously every 6 hours.

8. Which is the most appropriate goal for J.H.'s BP reduction?
   A. Goal mean arterial pressure (MAP) reduction of 25% during the first 60 minutes.
   B. Goal MAP reduction of 50% during the first 60 minutes.
   C. Goal MAP reduction of 25% during the first 24 hours.
   D. Goal MAP reduction of 50% during the first 24 hours.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
   a. Task A: 1, 2, 4, 6
   b. Task B: 1, 2, 5
2. Domain 2: Therapeutics and Patient Management
   a. Task A: 1-3, 5, 6
   b. Task B: 1, 2, 4
   c. Task C: 1-4
3. Domain 3: Professional Practice
   a. Task A: 4
   b. Task B: 1, 2, 4

I. ADVANCED ADULT CARDIAC LIFE SUPPORT

A. Background
1. Foundation of advanced cardiac life support (ACLS) is effective and timely basic life support (BLS).
2. Sudden cardiac arrest (SCA) continues to be a leading cause of death in many parts of the world.
3. SCA can vary in etiology (noncardiac vs. cardiac), circumstances (unwitnessed vs. witnessed), and setting (in vs. out of hospital).
4. Because of heterogeneity, action links that are denoted the "chain of survival" were developed for guidance (Circulation 2016;133:447-54). There is an increased recognition in the differences between arrests that occur in the hospital and those that do not, which has led to two distinct chains of survival:
   a. In-hospital cardiac arrest (IHCA) chain of survival
      i. Appropriate surveillance and early warning systems (prevention)
      ii. Activation of multidisciplinary response team
      iii. Early CPR that emphasizes chest compressions
      iv. Rapid defibrillation, if indicated
      v. Advanced life support and post-cardiac arrest care
      vi. Recovery
   b. Out-of-hospital cardiac (OHCA) arrest chain of survival
      i. Immediate recognition of SCA and activation of emergency response system
      ii. Early CPR that emphasizes chest compressions
      iii. Rapid defibrillation, if indicated
      iv. Basic and advanced emergency medical services
      v. Advanced life support and post-cardiac arrest care
      vi. Recovery
5. Following the chain of survival effectively can improve survival (e.g., with out-of-hospital, witnessed VF arrest, survival rates can approach 50%) (Circulation 2006;114:2760-5). Because BLS and ACLS are often experienced as a team approach in the hospital setting, it is imperative that hospital providers be familiar with all aspects of BLS and ACLS in order to fulfill any role during the arrest situation.

B. Basic and advanced emergency medical services
1. Immediate recognition of SCA and activation of emergency response system (IHCA and OHCA - chain of survival): Unresponsive patient or witnessed sudden collapse with absent or gasping abnormal breathing (Circulation 2016;133:447-54; Acad Emerg Med 2007;14:877-83).
   a. Ensure that the scene is safe.
   b. Check for response by tapping on shoulder and shouting at patient; simultaneously check for normal breathing.
   c. Activate emergency response system (e.g., calling 911), and follow instructions from trained dispatchers/responders (Ann Emerg Med 1993;22:354-65). In the IHCA setting, this would include the activation of the emergency response team.
2. Early CPR. Follow the sequence of C-A-B (compressions-airway-breathing) (IHCA and OHCA - chain of survival).
   a. C - Chest compressions are an essential component of CPR.
      i. Not often provided by nonmedical individuals until professional emergency responders arrive (Circ Cardiovasc Qual Outcomes 2010;3:63-81).
      ii. Both an increase in intrathoracic pressure and a direct compression of the heart lead to perfusion and oxygen delivery to the brain and myocardium.
      iii. In OHCA not observed by emergency responders, immediate bystander chest compressions improve survival over conventional CPR, stressing the importance of early chest compressions on survival outcomes (Bobrow 2010).

iv. All patients with SCA should receive chest compressions (Acta Anaesthesiol Scand 2008;52:914-9).

v. Place patient on a hard surface, use backboard (unless it will cause interruptions in chest compressions, delay in initiation of CPR, or dislodgment of lines/tubing), and/or deflate air-filled mattresses (J Intensive Care Med 2009;24:195-9; Acta Anaesthesiol Scand 2007;51:747-50; Resuscitation 2004;61:55-61).

vi. Perform high-quality chest compressions at a rate of 100–120 compressions per minute at a depth of 2–2.4 inches, and allow chest recoil after each compression. High-quality chest compressions optimize coronary perfusion, cardiac index, myocardial blood flow, and cerebral perfusion (Crit Care Med 2010;38:1141-6; Resuscitation 2006;71:137-45; Resuscitation 2006;71:341-51; Circulation 2015;132(suppl 2):S315-S367).

vii. Without the use of a compression feedback device, it may be difficult to judge compression rate and depth. In a randomized study, compression feedback devices were shown to increase adherence to CPR guidelines, increase CPR quality, increase rates of ROSC, and decrease injury (e.g., rib fractures) seen with CPR (Crit Care 2016;20:147:1-8).

viii. Actual number of chest compressions given per minute is a function of the compression rate and proportion of time without interruption. Goal is to minimize interruptions to chest compressions.
    (a) Increasing the number of compressions given per minute can increase the rate of ROSC, increase survival rates, and increase rates of neurologically-intact survival (JAMA 2008;299:1158-64; Circulation 2009;120:1241-7; Circulation 2005;111:428-34).
    (b) Rescuer fatigue is common and may lead to inadequate compression quality (Resuscitation 2009;80:918-4). It is recommended to change compressors every 2 minutes (or after five cycles of compressions at a rate of 30:2 compressions/ventilations) with no more than 10 seconds between changes (Resuscitation 2009;80:1015-8).
    (c) Pulse checks (including initial) should last no more than 10 seconds.
    (d) Duration of the single longest interruption to chest compressions (regardless of reason) is negatively associated with survival (Circulation 2015;132:1030-7), reemphasizing the need to minimize interruptions to chest compressions.
    (e) Compression-first (or “compression only” or “hands only”) CPR decreases time until first compression (Resuscitation 2004;62:283-9) and for suspected OHCA is acceptable for nonmedical rescuers (Circulation 2015;132(suppl 2):S315-S367).
    (f) A Cochrane review found that bystander-administered chest compression-only CPR (supported by telephone instruction) increases the number of people who survive to hospital discharge (Cochrane Database Syst Rev 2017;3:CD010134). It is unclear how well neurologic function is preserved in this population.

ix. Mechanical chest compression devices have not been shown to be superior to conventional CPR. They can be considered when prolonged CPR is necessary, or high-quality manual CPR is not available, being mindful of interruptions in CPR during device deployment and removal (Circulation 2015;132(suppl 2):S315-S367). A Cochrane review confirmed that mechanical chest compressions are not superior to manual chest compressions (Cochrane Database Syst Rev 2018;8:CD007260). Furthermore, in shockable rhythms, mechanical chest compression devices may lead to longer times to first defibrillation and greater intervals between additional defibrillations (Resuscitation 2017;115:155-62).

x. Data suggest that patients can have ROSC with meaningful neurological recovery even after prolonged (>25 min) pre-hospital resuscitation efforts (Circulation 2016;133:1386-96; Resuscitation 2016;105:45-51), so extended CPR efforts can be anticipated.

xi. The use of extracorporeal CPR is emerging as a therapy for those who fail conventional CPR. The current data seems promising in benefiting neurologic outcomes but is limited by bias and quality (Circulation 2019;140:e881-e894; Circulation 2024;149:e254-73). Current recommendation is that extracorporeal CPR may be considered for selected patients as rescue therapy when conventional CPR efforts are failing in settings in which it can be successfully implemented by skilled providers.

xii. Partial pressure of end-tidal CO_2 ($PETCO_2$), coronary perfusion pressure (aortic diastolic pressure minus right atrial diastolic pressure), arterial relaxation pressure, regional cerebral oxygenation and central venous oxygen saturation ($Scvo_2$) may correlate with cardiac output and myocardial blood flow during CPR. Threshold values have been reported at which ROSC is rarely achieved, and an abrupt increase in any of these variables is a sensitive indicator of ROSC (Table 1 - Circulation 2015;132(suppl 2):S315-S367; Ann Emerg Med 1992;21:1094-101; JAMA 1990;263:1106-13; Am J Emerg Med 1985;3:11-4; J Emerg Med 2010;38:614-21; Crit Care 2008;12:R115; Crit Care Med 2016;44:1663-74).

Table 1. Useful Physiological Variables During CPR

Variable	ROSC Rarely Achieved
$PETCO_2$	< 10 mm Hg
Coronary perfusion pressure	< 15–20 mm Hg
Arterial relaxation (diastolic) pressure	< 20–40 mm Hg
Regional cerebral oxygenation	< 25%
$Scvo_2$	< 30%

Patient Case

1. A.C., a 50-year-old man with a history of gastroesophageal reflux disorder and chronic obstructive pulmonary disease, was admitted for shortness of breath, palpitations, and presumed exacerbation of his lung disease. On hospital admission day 4, A.C. has a witnessed cardiac arrest on the family medicine unit. The emergency response team of which you are part is called, and when you arrive, the bedside nurse has already begun chest compressions. Which insight would be best shared regarding chest compressions for A.C.?

   A. Because the nurse has already begun chest compressions, she should continue chest compressions for the duration of CPR.

   B. Compressions increase intrathoracic pressure and directly compress the heart, which can generate cardiac output and deliver oxygen.

   C. Because increasing the intrathoracic pressure is vital to oxygen delivery, chest recoil is unnecessary and should be avoided.

   D. Number of chest compressions per minute does not affect outcomes, so pulse check and line and airway placements can interrupt chest compressions.

b. A - Airway

i. To place an artificial airway in patients without an advanced airway, use the head-tilt, chin-lift technique if patients have no evidence of head or neck trauma and the jaw thrust alone if cervical spine injury is suspected (JACEP 1976;5:588-90; JAMA 1960;172:812-5) (see "Rescue Breaths" following).

- ii. Cricoid pressure is the technique of applying pressure to the patient's cricoid cartilage to push the trachea posteriorly and compress the esophagus with the goal of preventing aspiration.
    - (a) May help in visualizing vocal cords during tracheal intubation.
    - (b) Recommend against use for adult cardiac arrest because of possible delay or prevention of advanced airway, lack of protection from aspiration, and lack of mastery from "expert" and nonexpert rescuers (Emerg Med Australas 2005;17:376-81; Br J Anaesth 1994;72:47-51).
- iii. If a foreign body airway obstruction (FBAO) occurs:
    - (a) Observe the patient with a mild FBAO. Mild FBAO is defined by a patient with a partial airway obstruction that is still able to talk and has an effective cough.
    - (b) Signs of severe FBAO include a silent cough, stridor, or increasing respiratory difficulty. If these occur, ask the patient, "Are you choking?" If the patient clutches their neck (universal sign of choking) or nods without answering verbally, consider severe FBAO:
        - (1) Activate the emergency response system.
        - (2) Administer abdominal thrusts to nonobese adults.
        - (3) In adults with obesity or women in the late stage of pregnancy, administer chest thrusts.
    - (c) If the patient becomes unresponsive:
        - (1) Place on ground and begin CPR as chest compressions have been shown to generate higher airway pressure than abdominal thrusts (Resuscitation 2000; 44:105-8).
        - (2) Each time the airway is opened during CPR to provide a rescue breath, look for an object in the patient's mouth and, if found, remove it. If not found, continue giving the rescue breaths (two total breaths), followed by 30 chest compressions.
        - (3) No studies have evaluated the routine use of the finger sweep to clear an airway in the absence of visible airway obstruction. Case reports have shown some efficacy, but harm has also been demonstrated in patients and rescuers. A finger sweep should not be used in the absence of visible airway obstruction.

c. B - Rescue breaths

- i. Primary purpose is to assist in maintaining oxygenation, with secondary purpose of eliminating carbon dioxide (CO_2).
- ii. Compressions should always be initiated first as the arterial oxygen content of blood remains unchanged until CPR is initiated.
- iii. Optimal compression/ventilation ratio, inspired oxygen concentration, tidal volume, and RR are yet to be determined.
- iv. Compression-only CPR without rescue breaths is recommended for nonmedical rescuers for OHCA (see earlier text for more detail). Trained nonmedical rescuers are encouraged to perform rescue breaths at a ratio of 30 compressions to 2 breaths. When the patient has an advanced airway in place during CPR, rescuers no longer deliver cycles of 30 compressions and 2 breaths (i.e., they no longer interrupt compressions to deliver 2 breaths). Instead, the provider may reasonably deliver 1 breath every 6 seconds (10 breaths/minute) using bag-mask ventilation while continuous chest compressions are being performed (Circulation 2015;132(suppl 2): S414-35).
    - (a) Low minute ventilation (low tidal volume and/or low RR) can maintain oxygenation and ventilation during CPR as there is low oxygen uptake at the tissues and low CO_2 production (Circulation 1997; 95:1635-41).
    - (b) Give sufficient tidal volume to produce visible chest rise (Resuscitation 1996;31:231-4). Excessive ventilation can increase intrathoracic pressure and decrease venous return as well as cause gastric inflation, which can lead to aspiration, regurgitation, and decreased survival (Circulation 2004;109:1960-5; Resuscitation 1998;36:71-3; JAMA 1987; 257:512-5).

- (c) Continuous chest compressions with asynchronous ventilation compared with chest compressions with interruptions for synchronous ventilation have not demonstrated improved outcomes when delivered by emergency medical services (N Engl J Med 2015;23:2203-14).

v. Deliver each rescue breath over 1 second. Mouth-to-mouth, mouth-to-barrier, mouth-to-stoma, and mouth-to-nose variations in initial rescue breathing are all acceptable and can achieve adequate oxygenation and ventilation (Chest 1994;106:1806-10; Br J Anaesth 1964;36:542-9).

vi. Positive-pressure ventilation
  - (a) Bag-mask ventilation
    - (1) Components include a nonjam inlet valve, either no pressure relief valve or a pressure relief valve that can be bypassed, standard 15-mm/22-mm fittings, an oxygen reservoir to allow for high oxygen delivery, and a non-rebreathing outlet valve (Respir Care 1992;37:673-90; discussion 690-4).
    - (2) Should not be used by a single rescuer.
    - (3) Should use an adult bag (1 or 2 L) and deliver (two-thirds or one-third of bag volume, respectively) about 600 mL of tidal volume, which should produce chest rise, oxygenation, and normocarbia (Resuscitation 2005;64:321-5; Resuscitation 2000;43:195-9).
    - (4) Quantitative waveform capnography with a bag-mask device to confirm and monitor CPR quality is now recommended. Prior to the 2020 guidelines, the recommendation for quantitative waveform capnography monitoring was limited to monitoring only after endotracheal tube placement (https://acls-algorithms.com/2021-aha-acls-guideline-changes/adult-cardiac-arrest-algorithm-changes/)
  - (b) Supraglottic airway devices (e.g., King Airway device) are considered an acceptable alternative to bag-mask ventilation during cardiac arrest (assuming proper training is supplied to rescuer) (Circ J 2009;73:490-6; Prehosp Emerg Care 1997;1:1-10).
    - (1) In OHCA, supraglottic airway devices may be associated with an increased rate of ROSC and faster time to airway placement, but survival outcomes are uncertain (Crit Care Med 2024;52:e89-99).
    - (2) Supraglottic airway devices are considered within the scope of BLS in some geographical regions.
  - (c) See the ACLS section for more details and information regarding endotracheal intubation.

vii. Naloxone for opioid-related life-threatening emergencies: Has an independent algorithm in the most recent guidelines (Circulation 2020;142(16_suppl_2):S366-468).
  - (a) Should be considered when a pulse is present but the patient has abnormal breathing or gasping (e.g., respiratory arrest).
  - (b) Can consider (in addition to BLS) administration of intramuscular or intranasal naloxone.
  - (c) If patients lose their pulse, provision of CPR should commence with continued consideration of naloxone if opioid intoxication is suspected.
  - (d) Administer 0.4 mg intramuscularly or 2 mg intranasally diluted in 3 mL of normal saline – may repeat dose every 4 minutes.

Patient Case

2. L.S. is a 66-year-old woman visiting her husband at the hospital on the hospice unit. She is buying lunch in the cafeteria, and while in line to check out, she collapses. The emergency response team of which you are part is summoned. L.S. does not respond to voice or tapping of the shoulder, and a brief look at her chest shows no chest movement. Chest compressions are initiated while the crash cart and defibrillator are retrieved. Of note, a bag-mask ventilator is available at the scene because it is carried with the emergency response team. Which is most accurate about L.S.'s airway and breathing management?

   A. A compression/ventilation ratio of 15:2 should be used throughout resuscitation efforts.
   B. Because it is a multiple-rescuer scene, bag-mask ventilation should not be used because it is recommended only in single-rescuer resuscitations.
   C. Rescue breaths should be given at a ratio of 30 compressions to 2 breaths, avoiding excessive ventilation given as synchronous ventilations.
   D. Bag-mask ventilation should not be used in any patient because advanced airways are preferred to supply oxygen and eliminate CO_2.

3. Rapid defibrillation with a manual or automated external defibrillator (AED) (IHCA and OHCA - chain of survival)
   a. Defibrillation shock = unsynchronized shock.
   b. Successful defibrillation is defined as 5 seconds or greater of termination of arrhythmia after a shock is delivered.
   c. Early defibrillation of VF is crucial because it is the most common rhythm in witnessed OHCA, survival diminishes rapidly over time, and VF often progresses to asystole (Resuscitation 2000;44:7-17; Circulation 1997;96:3308-13).
   d. Three key actions must occur within moments of VF SCA to increase the likelihood of survival: (1) activation of the emergency medical services system (e.g., emergency response team), (2) provision of CPR, and (3) shock delivery (Ann Emerg Med 1993;22:1652-8).
   e. Performing chest compressions while a defibrillator is obtained significantly improves the probability of survival (Circulation 2009;120:1241-7). When VF is present for more than a few minutes, the myocardium becomes depleted of oxygen and energy substrates (e.g., adenosine triphosphate [ATP]) (Grover 1977).
      i. CPR can provide the oxygen and ATP needed until the shock is delivered.
      ii. Increased likelihood of termination of VF from shock delivery and ROSC if CPR given first (Circulation 2004;110:10-5).
      iii. If CPR is initiated immediately, survival can double or triple at most time intervals until defibrillation occurs (Resuscitation 2000;44:7-17; Ann Emerg Med 1995;25:780-4; Ann Emerg Med 1993;22:1652-8).
   f. Early defibrillation is a powerful predicator of ROSC after VF.
      i. Survival rates are highest for VF when CPR and defibrillation occur within 3–5 minutes of the event (Circ Cardiovasc Qual Outcomes 2010;3:63-81; Resuscitation 2009;80:1253-8). In the IHCA setting, prompt defibrillation (less than 2 minutes from the VF event) was associated with higher rates of long-term survival (Circulation 2018;137:2041-51).
         (a) For every minute that passes after collapse, survival from VF decreases 7%–10% (Ann Emerg Med 1993;22:1652-8).
         (b) CPR prolongs VF and delays the progression to asystole (Resuscitation 2000;47:59-70; Am J Emerg Med 1985;3:114-9).

- ii. CPR should be initiated immediately, with shock delivery as soon as possible.
- iii. One-shock biphasic (bidirectional) shock protocols are better than or equivalent to three-shock monophasic (one-directional) stacked protocols in terminating VF.
    - (a) Almost all AEDs manufactured currently are biphasic.
    - (b) Polyphasic waveform defibrillators are currently under investigation. Double-sequential defibrillation is not supported (Circulation 2020;142:S366-S468).
- iv. With any shock delivery, chest compressions should resume immediately, and pulse check should be delayed until the end of the next cycle of CPR because this can increase successful defibrillation with ROSC (Circulation 2004;110:10-5; Circulation 2002;105:2270-3).
- v. The optimal shock energy for biphasic first shock has yet to be determined.
    - (a) Low-energy dosages (200 J or less) are safe and have equivalent or higher efficacy of termination of VF than monophasic waveform shocks at the same or higher energy (Circulation 2007;115:1511-7; Prehosp Emerg Care 2000;4:305-13).
    - (b) The energy dosage used should be according to the manufacturer's recommendation (e.g., 120 or 200 J).
- vi. If additional shocks are needed, it is recommended that at least equivalent and potentially higher energy be used for subsequent shocks. Double-sequential defibrillation – shock delivered by two defibrillators almost simultaneously – is a new approach, but a systematic review has failed to establish its efficacy in resuscitation (Circulation 2020;142(suppl 1):S92-S139).
- vii. Electrode placement
    - (a) Pad positioning is equally effective in terminating ventricular arrhythmias in four positions: anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular (Medicina (Kaunas) 2006;42:994-8; Physiol Meas 2006;27:1009-22).
    - (b) Lateral pads should be placed under breast tissue, and hirsute men should be shaved before the placement of pads.
    - (c) In patients with an implantable cardioverter-defibrillator or a pacemaker, it may be beneficial to avoid placing the pads or paddles over the device.
    - (d) Do not place the pads on top of a medication patch because this can cause current impedance or burning of the skin (Am J Emerg Med 1992;10:128-9).
- viii. In-hospital AED use should be considered in ambulatory and unmonitored areas.

g. Pulseless VT (pVT) is treated like VF.

h. Pacing is not recommended for unstable VF or pVT (Circulation 2010;122:S685-705).

Patient Case

3. T.V. is a 72-year-old man with a history of chronic liver disease, hypoglycemia, and atrial fibrillation. He was admitted to the medical intensive care unit (MICU) 2 days ago for sepsis requiring aggressive fluid resuscitation and intravenous antibiotics. T.V. did not require vasopressors to treat his sepsis. On ICU day 3, T.V. develops VF on telemetry, loses consciousness, and becomes pulseless; the MICU team is summoned for a presumed VF cardiac arrest. Pads are placed on T.V. by the time the team arrives, and the rhythm is confirmed to be VF. Which is the most accurate statement regarding defibrillation for T.V.?
   - A. Three vital actions with VF can lead to increased survival if they occur rapidly: activate emergency response system, provide CPR, and deliver shock.
   - B. T.V. should not be defibrillated but should be paced out of the VF, if possible, because pacing is more effective for pulseless VF.
   - C. Chest compressions should be delayed until the defibrillator is charged because defibrillation is the definitive treatment of VF.
   - D. Alternative treatments such as antiarrhythmics, vasopressors, and magnesium should be tried first.

C. ACLS Interventions
   1. Airway control and ventilation
      a. Background
         i. During CPR, oxygen delivery to the heart and brain becomes more flow-dependent than arterial oxygen saturation–dependent (Ann Emerg Med 1990;19:1104-6).
         ii. Placement of an advanced airway in cardiac arrest should not delay CPR or defibrillation.
         iii. No studies address the optimal timing of advanced airway placement. The guiding general concept is to place the advanced airway while minimizing interruptions to chest compressions.
         iv. Conflicting evidence exists for the urgent placement of an advanced airway.
            (a) Study of IHCA has shown an increased 24-hour survival in patients with an advanced airway placed within 5 minutes. No difference was found regarding ROSC (Resuscitation 2010;81:182-6); however, another study has shown a worse overall survival rate in cardiac arrest patients who required intubation (Arch Intern Med 2001;161:1751-8).
            (b) OHCA studies have shown that intubation in the rural and urban setting and, more specifically, intubation within 13 minutes, is associated with better survival (Med J Aust 2006;185:135-9; Prehosp Emerg Care 2004;8:394-9).
            (c) One large randomized controlled trial comparing endotracheal intubation to bag-mask ventilation in OHCA found no difference in 28-day survival with favorable neurological function (JAMA 2018;319:779-87).
      b. Oxygen during CPR
         i. Unclear what the optimal concentration of inspired oxygen content should be during CPR, but it is currently recommended that maximum (e.g., 100%) inspired oxygen be used to optimize arterial oxyhemoglobin content and, subsequently, oxygen delivery (Circulation 2015;132(suppl 2):S315-S367).
         ii. In OHCA, patients with a higher Pao_2 had higher survival to hospital admission but not neurologically intact survival, which is likely a function of the underlying pathophysiology (Resuscitation 2013;84:770-5).
         iii. Extended exposure to high oxygen concentrations carries the risk of toxicity, but this toxicity has not been shown in the short-term setting of adult CPR (Resuscitation 1999;42:221-9).

    iv. During chest compressions, air is forcefully expelled from the chest, and oxygen is drawn into the chest by passive recoil. Because the ventilation requirements are lower than normal, passive oxygen delivery is theorized to be sufficient for several minutes of initial CPR (Circulation 1994;90:3070-5), but recommendations to remove ventilation cannot be made.
c. Bag-mask ventilation: Viable option for oxygenation and ventilation during CPR but should be provided only when there is more than one rescuer and/or trained personnel (for more details, see earlier discussion) (Circulation 2010;122:S729-767).
d. Airway adjuncts
    i. *Cricoid pressure* should be used only in special circumstances to help visualize the vocal cords and should be relaxed, released, or adjusted if it impedes ventilation or advanced airway placement.
    ii. *Oropharyngeal airways* can be considered to help facilitate bag-mask ventilation in the unresponsive patient with no cough or gag reflex.
    iii. *Nasopharyngeal airways* can be considered in patients with airway obstruction and clenched jaw but should be used cautiously in craniofacial injury and avoided in known coagulopathy because of an increased risk of bleeding (J Trauma 2000;49:967-8; Anaesthesia 1993; 48:575-80).
e. Advanced airways
    i. Endotracheal intubation
        (a) Attempted placement by unskilled providers leads to unacceptably large periods of chest compression interruption and hypoxemia.
        (b) Benefits include keeping the airway patent, allowing for suctioning of airway, ensuring high oxygen concentration delivery, providing a third line medication administration option, allowing for specific tidal volume delivery, and providing protection from aspiration.
    ii. Supraglottic airways
        (a) Do not require visualization of glottis, which allow for continuous chest compressions.
        (b) Types studied during cardiac arrest include laryngeal mask airway, esophageal-tracheal tube (Combitube), laryngeal tube (laryngeal tube or King Airway LT), among others. No difference in successful prehospital ventilation, ROSC, or 1-month neurologic outcome between laryngeal mask airway and laryngeal tube for OHCA has been demonstrated (Am J Emerg Med 2015;33:1360-3).
        (c) When used by trained providers, they allow as effective oxygenation and ventilation as bag-mask ventilation and endotracheal intubation.
    iii. Recommendations regarding type of advanced airway are equivocal (Circulation 2019;140:e881-e894).
        (a) Supraglottic airways can be used for adults with OHCA in settings with low tracheal intubation success rate or minimal training opportunities for ETT placement.
        (b) Supraglottic airways or ETT can be used for adults with OHCA in settings with high tracheal intubation success rates or optimal training opportunities for ETT placement.
        (c) If an advanced airway is used in the in-hospital setting by expert providers trained in these procedures, either the supraglottic airway or ETT can be used.
        (d) Frequent experience/retraining is recommended for providers who perform endotracheal intubation.
        (e) Emergency medical services systems that perform prehospital intubation should provide a program of ongoing quality improvement.
    iv. After advanced airways are secured, proper placement should be confirmed with clinical assessment and objective measures without interruptions to chest compressions.

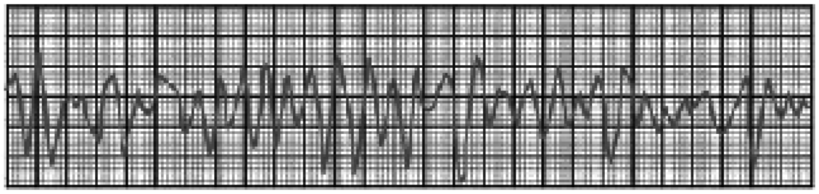
      - (a) Physical assessments include visually inspecting chest rise bilaterally and listening to the epigastrium (breath sounds should be absent) and lung fields (should be equal and adequate).
      - (b) Exhaled CO_2 or esophageal detector devices are a reasonable and objective means of confirmation if continuous waveform capnography is not readily available.
      - (c) Continuous waveform capnography is the most reliable and objective way to ensure, confirm, and monitor correct endotracheal tube placement. Although not specifically studied with supraglottic airways, readings should be similar to endotracheal readings.
      - (d) False-positive CO_2 detection (CO_2 detected not from ventilation) is rare, whereas false-negative CO_2 detection (no CO_2 detection when ventilation is occurring) is more common. Most common cause of false-negative CO_2 detection is a reduction in blood flow or CO_2 delivery to lungs (e.g., lack of quality chest compressions, pulmonary embolism, severe airway obstruction). Partial pressure of end-tidal CO_2 ($PETCO_2$) less than 10 mm Hg during CPR suggests ROSC is unlikely, and maneuvers such as improving the quality of chest compressions, adding vasopressor therapy, and others, should be considered.
    - v. Post-intubation airway management
      - (a) Airway should be marked (from front of teeth/gums) and secured (with tape or commercial device), avoiding compression around the neck, which could impair venous return from the brain.
      - (b) Chest radiography is suggested for confirmation of location of end of endotracheal tube in relation to the carina.
      - (c) Slower ventilator rates (6–12 breaths/minute) have been shown to improve hemodynamics and short-term survival in animal models of cardiac arrest (Crit Care Med 2006;34:1444-9; Circulation 2004;109:1960-5; Resuscitation 2004;61:75-82).
    - vi. After placement, continuous chest compressions should be given at a rate of 100-120 compressions per minute. A breath should be delivered every 6–8 seconds (8–10 breaths/minute), making sure to avoid over-ventilation, which could decrease venous return and cardiac output.

Patient Case

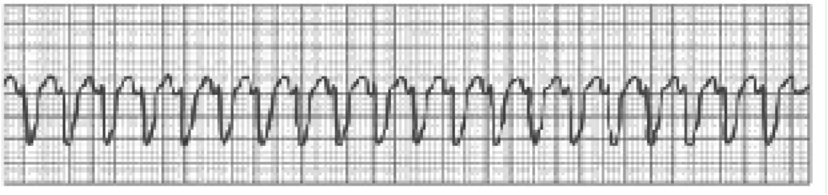
8. F.V. is a 63-year-old woman with a history of diabetes, heart failure with preserved ejection fraction, hypertension, and obstructive sleep apnea who presents to the ED with chest tightness and “feeling funny.” In the ED, F.V. loses consciousness and develops pVT. Chest compressions are initiated immediately, pads are placed, and bag-mask ventilation is given at a compression/ventilation ratio of 30:2 for two cycles. The monitor confirms the rhythm of pVT. The defibrillator is charged, the patient is cleared, and the first shock is delivered. Chest compressions resume, and during the next pulse check, the patient is intubated. F.V. still has no pulse, and chest compressions are continued. Which is the most accurate statement about F.V.’s resuscitation after advanced airway placement?

   A. The compression/ventilation ratio should remain 30:2 to avoid excessive ventilation.
   B. The advanced airway should have been placed before defibrillation and CPR for pVT.
   C. The patient should be placed on room air (21% FIO_2 [fraction of inspired oxygen]).
   D. Proper airway placement should be confirmed with clinical assessment and objective measures.

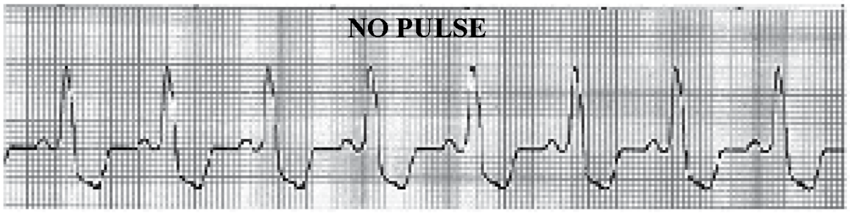
2. Management of cardiac arrest
   a. Background
      i. Cardiac arrest can be caused by four primary "rhythms": VF, pVT, PEA, and asystole.
      ii. These rhythms can also be classified as shockable (VF and pVT) and non-shockable (PEA and asystole).
         (a) Ventricular fibrillation
            (1) Wide complex
            (2) Polymorphic
            (3) Disorganized
            (4) Coarse or fine
            (5) No/minimal forward flow



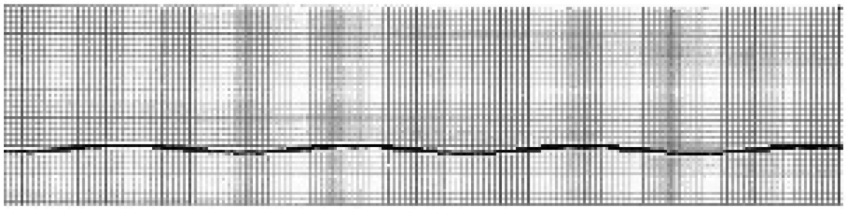
         (b) Pulseless VT
            (1) Wide complex
            (2) Monomorphic or polymorphic
            (3) Generally organized
            (4) No/minimal forward flow



         (c) Pulseless electrical activity
            (1) Not a rhythm itself but defined as an organized rhythm that would be expected to produce mechanical activity but does not
            (2) Absent or insufficient mechanical ventricular activity
            (3) No/minimal forward flow



         (d) Asystole (ventricular asystole)
            (1) Absence of detectable ventricular electrical activity
            (2) Accompanied by absence of ventricular mechanical activity
            (3) No/minimal forward flow



iii. Survival requires both BLS and ACLS. Foundation of ACLS is high-quality BLS. In addition to CPR, the only proven rhythm-specific therapy that increases survival at hospital discharge is defibrillation of VF/pVT.

iv. Medications have not consistently been shown to increase survival of cardiac arrest but have been shown to increase the rate of ROSC or survival to hospital admission (Resuscitation 2010;81:182-6; Med J Aust 2006;185:135-9; Resuscitation 2000;45:161-6; N Engl J Med 1999;341:871-8).

  (a) Vascular access and medication delivery should never interrupt CPR and/or defibrillation. All other therapies are "considerations" and should never compromise chest compressions.

  (b) If interruptions in chest compressions are necessary (e.g., rhythm assessment, delivery of defibrillation shocking in VF/VT), recommendation is to minimize duration (less than 10 seconds).

v. During cardiac arrest treatment, it is imperative to evaluate, treat, and/or reverse any treatable causes of cardiac arrest (Table 2).

vi. Post–cardiac care should begin immediately after ROSC is obtained to avoid re-arrest.

Table 2. Treatable Causes of Cardiac Arrest

H's	T's
Hypoxia	Toxins
Hypovolemia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Thrombosis • Pulmonary embolism • Coronary thrombosis
Hypoglycemia	
Hypo/hyperkalemia	Tension pneumothorax
Hypothermia	

Patient Case

4. V.B., a 62-year-old man with an unknown medical history, comes to your ED altered and incoherent. He is admitted to the ED for observation, where he suddenly becomes unconscious and pulseless. The ED staff immediately initiates CPR for V.B., who is found to be in PEA. Which statement best describes appropriate cardiac arrest treatment?

   A. Survival from PEA is solely dependent on medications and advanced airways, so airway intubation and line placement take priority over CPR.
   B. The treatable causes of PEA cardiac arrest should be reviewed and addressed while CPR and laboratory tests are sent.
   C. Because the patient is in PEA, pads should be placed, the patient cleared, and shock delivered immediately.
   D. No strategies exist for post-arrest care to avoid re-arrest or improve outcomes from the PEA cardiac arrest.

b. Medication background (rhythm independent considerations)
   i. Goal: Increase myocardial blood flow during CPR and help achieve ROSC
   ii. Drug delivery
      (a) Central intravenous administration is recommended, if available. Central line placement should not interrupt CPR. The advantage of central administration is higher peak concentration and shorter drug circulation times than with peripheral routes (Crit Care Med 1988;16:1138-41; Ann Emerg Med 1981;10:73-8; Ann Emerg Med 1981;10:417-9).
      (b) If peripheral administration of medications is necessitated, a bolus injection should be followed by a 20-mL bolus of an intravenous fluid (e.g., 0.9% sodium chloride) to facilitate drug flow from the extremity to the central circulation (Am J Emerg Med 1990;8:190-3).
      (c) If proximal humerus intraosseous (IO) access is used, administration and drug delivery are similar to central venous access. If proximal or distal tibial intraosseous access is used, administration and drug delivery are similar to peripheral venous access and would necessitate a 20-mL bolus or pressure bag to facilitate drug administration. In a randomized cadaver study, tibial IO access has been shown to be easier to obtain, which allows for faster medication administration (Medicine 2016; 95: e3724). Data analyses suggest that intraosseous access is associated with poorer OHCA survival and fewer favorable neurologic outcomes, even after controlling for many other variables (Ann Emerg Med 2018;71:588-96). Intraosseous access may have initially been selected by first responders because of perceived complexity and influential patient characteristics. However, additional analysis has found that tibial intraosseous access compared with intravenous access is associated with a lower likelihood of ROSC and survival to hospitalization (Resuscitation 2017;117:91-6). The most recent guidelines now support the use of intravenous access preferentially unless it cannot be obtained (Circulation 2020;142:S366-S468). In these circumstances, intraosseous access is reasonable.
      (d) Endotracheal (ET) delivery
         (1) NAVEL acronym summarizes medications that have been studied and shown to have tracheal absorption by ET tube delivery. N – naloxone, A – atropine, V – vasopressin, E – epinephrine, L – lidocaine.
         (2) Serum concentrations of medications are lower when given by ET delivery.
         (3) Optimal ET doses unknown; typically, they are 2–2.5 times intravenous doses but may be higher (e.g., up to 3–10 times higher for epinephrine) (Crit Care Med 1987;15:1037-9).
         (4) Should be diluted with either 5–10 mL of 0.9% sodium chloride or sterile water and injected directly into the ET tube, ideally during pulse check to avoid medication expulsion back out the ET (Crit Care Med 1994;22:1174-80)
      (e) Peak effect of intravenous or intraosseous medication delayed 1–2 minutes during CPR.
      (f) Theoretical concern that giving high-dose bolus vasopressors after ROSC following defibrillation may precipitate cardiac instability and re-arrest. May be avoided by using physiological monitoring such as quantitative waveform capnography, intra-arterial pressure monitoring, or continuous central venous oxygen saturation monitoring and avoiding administration of vasopressors if ROSC occurs (J Emerg Med 2009;38:614-21; Ann Emerg Med 1992;21:1094-101; Ann Emerg Med 1990;19:1104-6).

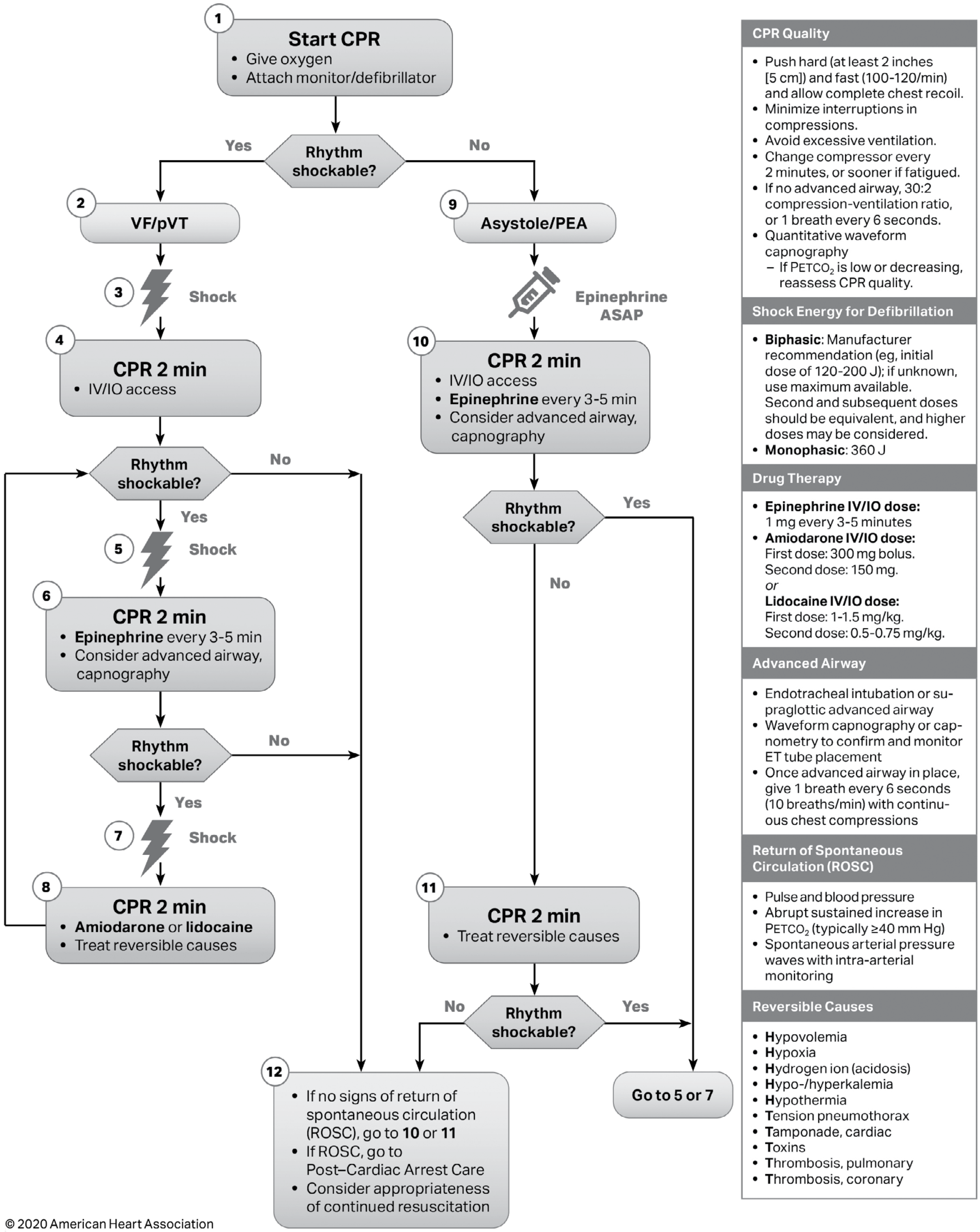
Patient Case

5. M.G., a 58-year-old woman with a history of chronic osteoarthritis and peptic ulcer disease, is admitted to the MICU with hypovolemic shock caused by a suspected bleeding gastric ulcer. Endoscopy is performed, confirming the gastric ulceration. The ulcer is cauterized, and M.G. is stabilized. On ICU day 2, M.G. becomes lethargic, hypoxic, and subsequently pulseless. The MICU team is summoned, and the monitor reveals VF. Resuscitation efforts begin, and the ACLS algorithm is followed. The patient will receive amiodarone. Which general principles are most accurate regarding amiodarone administration for M.G.'s VF arrest?
    A. Endotracheal delivery is preferred because all cardiac arrest medications can be delivered by the endotracheal route.
    B. Peripheral administration is preferred because the peak concentrations are higher and the circulation time is shorter than with other routes.
    C. Intraosseous administration is preferred because administration and dosing are similar to that for the endotracheal route.
    D. Central intravenous administration is preferred because the peak concentration and circulation time is shorter than with other routes.

c. Management of VF/pVT (Figure 1): Defibrillation (summary, details available previously in the IHCA and OHCA chain of survival: Defibrillation section)
    i. When VF/pVT detected, CPR should continue until defibrillator (either manual or automatic) charging period is over.
    ii. It is strongly recommended that CPR be performed while the defibrillator is readied because chest compressions can deliver oxygen and potentially unload the ventricles, increasing the likelihood that a perfusing rhythm will return after shock is delivered.
    iii. Because intentionally delaying defibrillation for CPR has mixed results, it cannot currently be recommended.
    iv. Once defibrillator is charged, patient is "cleared" (ensuring all members of the resuscitation team are no longer in contact with the patient).
    v. Shock is delivered, and CPR is immediately resumed, beginning with chest compressions.
        (a) Pulse check is delayed until 2 minutes of CPR is given.
        (b) Pause for rhythm and pulse check (less than 10 seconds); continue CPR, if necessary.
    vi. If biphasic defibrillator is available:
        (a) Provider should use manufacturer's recommended energy dose (e.g., 120–200 J).
        (b) If information unavailable, the maximum dosing can be considered.
        (c) Second and subsequent defibrillator energy dosages should be equivalent, and consideration should be made for escalating energy doses, if possible.
    vii. If monophasic defibrillator is the only available defibrillator:
        (a) Initial energy dose should be 360 J.
        (b) Second and subsequent defibrillator energy dosages should be 360 J.
    viii. If VF/pVT is terminated by defibrillation and reoccurs, resulting in an arrest, the successful energy dosage used previously should be considered.
    ix. Change of multimodal defibrillator from automatic to manual mode may result in fewer interruptions of CPR but also an increased frequency of inappropriate shocks (Resuscitation 2007;73:131-6; Resuscitation 2007;73:212-20).

d. Medication therapy for VF/pVT
  i. Previous guidelines suggested medication consideration after one shock and 2 minutes of CPR (one cycle). Data from witnessed OHCA suggest that early administration of epinephrine is associated with improved survival in shockable rhythms (Resuscitation 2015;96:180-5) and that every minute beyond 5 minutes significantly increases the odds of death. With IHCA for shockable rhythms, patients receiving epinephrine within 2 minutes of initial shock was associated with a decreased odds of survival, ROSC, and good functional outcome (BMJ 2016;353:i1577). Guideline recommendation supports the use of epinephrine for shockable rhythms after two initial defibrillation attempts have failed (Circulation 2019;140:e881-e894).
  ii. Vasopressors:
    (a) First-line medication is epinephrine. A randomized, double-blind, placebo-controlled trial showed that use of epinephrine in OHCA (around 20% shockable rhythms) was associated with greater 30-day survival, but there was no difference in neurologically favorable outcomes because of the severe neurologic impairment of survivors (N Engl J Med 2018;379:711-21).
      (1) A meta-analysis of randomized controlled trials found that epinephrine (1 mg every 3–5 minutes) when compared to placebo for OHCA increased rate of ROSC, survival to hospital admission and survival to hospital discharge but did not change discharge with favorable neurological function (Resuscitation 2019;139:106-21). The administration of epinephrine 1 mg every 3–5 minutes has been the standard medication within the cardiac arrest algorithm. An option to provide epinephrine every 4 minutes as a midrange has been added. This allows the provider to administer epinephrine every other 2-minute rhythm check (https://acls-algorithms.com/2021-aha-acls-guideline-changes/adult-cardiac-arrest-algorithm-changes/).
      (2) The traditional dose of epinephrine is considered 1 mg. Data analyses suggest that lower doses (e.g., 0.5 mg) are not associated with a change in survival to hospital discharge or favorable neurologic outcomes (Resuscitation 2018;124:43-8).
      (3) High-dose epinephrine (0.1–0.2 mg/kg) has been investigated and although it may increase the rate of ROSC, it has not been found to increase rate of survival to hospital admission, survival to hospital discharge, or survival with favorable neurological function (Circulation 2019;140:e881-e894).
    (b) Vasopressin has previously been removed from guidelines because of an equivalence of effect with epinephrine and a drive to simplify treatment (Figure 1; Table 3). A meta-analysis affirms the equivalence of vasopressin with epinephrine (either in isolation or in combination), supporting the recommendation that vasopressin offers no advantage over epinephrine in cardiac arrest (Resuscitation 2019;139:106-21).
    (c) No other vasopressors (e.g., phenylephrine or norepinephrine) have shown any benefit compared with epinephrine (JAMA 1992;268:2667-72; Acta Anaesthesiol Scand 1985;29:610-3).
    (d) Adding methylprednisolone and vasopressin to epinephrine during ACLS plus stress dose hydrocortisone for post-ROSC shock compared with placebo may aid in ROSC during cardiac arrest and improve neurologic function at discharge. Role of steroids may be debated, given the addition of vasopressin in the study arm (JAMA 2013;310:270-9). A network meta-analysis suggests that the combination of vasopressin-steroids-epinephrine was the only vasopressor regimen associated with ROSC and, in IHCA, also survival (Crit Care Med 2018;46:e443-e451). Guidelines suggest this treatment bundle may be considered, but further confirmatory data are needed (Circulation 2015;132(suppl 2):S315-S367). Newer evidence suggests this bundle may improve the chances of ROSC, but is not powered to assess survival outcomes (Andersen 2021).

Adult Cardiac Arrest Algorithm


1
Start CPR
• Give oxygen
• Attach monitor/defibrillator
Yes
Rhythm shockable?
No
2
VF/pVT
9
Asystole/PEA
3
Shock
Epinephrine ASAP
4
CPR 2 min
• IV/IO access
10
CPR 2 min
• IV/IO access
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
No
Yes
Rhythm shockable?
Yes
5
Shock
No
6
CPR 2 min
• Epinephrine every 3-5 min
• Consider advanced airway, capnography
Rhythm shockable?
No
Yes
7
Shock
8
CPR 2 min
• Amiodarone or lidocaine
• Treat reversible causes
11
CPR 2 min
• Treat reversible causes
No
Rhythm shockable?
Yes
12
• If no signs of return of spontaneous circulation (ROSC), go to 10 or 11
• If ROSC, go to Post–Cardiac Arrest Care
• Consider appropriateness of continued resuscitation
Go to 5 or 7

CPR Quality

- Push hard (at least 2 inches [5 cm]) and fast (100-120/min) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Change compressor every 2 minutes, or sooner if fatigued.
- If no advanced airway, 30:2 compression-ventilation ratio, or 1 breath every 6 seconds.
- Quantitative waveform capnography
  - If $PETCO_2$ is low or decreasing, reassess CPR quality.

Shock Energy for Defibrillation

- **Biphasic**: Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic**: 360 J

Drug Therapy

- **Epinephrine IV/IO dose:** 1 mg every 3-5 minutes
- **Amiodarone IV/IO dose:** First dose: 300 mg bolus. Second dose: 150 mg.

  or

  Lidocaine IV/IO dose: First dose: 1-1.5 mg/kg. Second dose: 0.5-0.75 mg/kg.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 seconds (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Abrupt sustained increase in $PETCO_2$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

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Figure 1. Adult cardiac arrest algorithm. CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); IV = intravenous(ly); PEA = pulseless electrical activity; $PETCO_2$ = partial pressure of end-tidal CO2; pVT = pulseless ventricular tachycardia; VF = ventricular fibrillation.

(e) Prehospital methylprednisolone in primarily shockable rhythms was studied in a phase II study and demonstrated significant reductions in inflammatory markers associated with post-cardiac arrest syndrome (Intensive Care Med 2024;49:1467-78). Further investigation may be warranted to determine the clinical impact of these findings.

iii. Antiarrhythmics:

(a) No evidence that, in cardiac arrest, any antiarrhythmics increase survival to discharge.

(b) Conflicting evidence on benefit of amiodarone and lidocaine (Table 3) in the prehospital arrest situation:

(1) Amiodarone or lidocaine may be considered for VF/pVT that is unresponsive to defibrillation (Circulation 2019;140:e881-e894).

(2) Investigation has found that amiodarone (300 mg) increased rates of survival to hospital admission compared to placebo in shock-refractory VF/pVT in those who received at least 3 shocks and epinephrine (N Engl J Med 1999;341:871-8). Additionally, 5 mg/kg amiodarone improved survival to hospital admission compared with 1.5 mg/kg lidocaine (N Engl J Med 2002;346:884-90). These 2 studies did not find evidence of improved survival to hospital discharge. Additionally, a comparison in patients with VF/pVT considered refractory after at least 1 shock, which found that ROSC was higher in patients receiving lidocaine compared with those receiving placebo, but not for those receiving amiodarone. Survival to hospital admission was higher with amiodarone or lidocaine compared to placebo, but no difference in survival with good neurological outcome or survival to hospital discharge in any group (N Engl J Med 2016;374:1711-22). These drugs may be particularly useful for patients with witnessed arrest, for whom time to drug administration may be shorter (Circulation 2019;140:e881-e894).

(3) Amiodarone should be administered as undiluted intravenous/intraosseous push if pulseless. Dosing should be 300 mg with repeat dosing of 150 mg (Table 3).

(4) If pulse is obtained, the suggested dose is 150 mg, which must be given as slow intravenous piggyback over at least 15 minutes and is typically followed by a continuous intravenous infusion.

(5) Hemodynamic effects of bradycardia and hypotension may be partly related to vasoactive solvents (polysorbate 80) (Am J Cardiol 2002;90:853-9).

(c) Magnesium sulfate (Table 3) is effective for cardiac arrest caused by torsades de pointes. (i.e., caused by early afterdepolarizations during phase 2 of the action potential).

(1) Not effective when VF/pVT is not associated with torsades de pointes.

(2) May consider for emergency magnesium replacement in patients who sustain cardiac arrest and are hypomagnesemic.

(3) Optimal dosing has not been established.

(d) In patients with non-shockable rhythms that become shockable in OHCA, investigation has shown some numeric benefit of antiarrhythmics, perhaps warranting further investigation in this patient group (Circulation 2017;136:2119-31).

Table 3. Medications Used During Sudden Cardiac Arrest

Medication	Primary Mechanism of Action in Cardiac Arrest	Dosage, Route, Frequency	Clinical Benefits
Epinephrine (N Engl J Med 1992;327:1045-50; Circulation 1984;69: 822-35; Crit Care Med 1979;7:293-6)	α-Adrenergic agonist effects leading to vasoconstriction	1 mg IV/IO q3–5 min 2–2.5 mg ET q3–5 min (diluted with either 5–10 mL of 0.9% sodium chloride or sterile water)	Increases coronary and cerebral perfusion pressure during CPR Increases ROSC Increases survival to hospital admission and discharge in OHCA
Amiodarone (N Engl J Med 2002;346:884-90; N Engl J Med 1999;341:871-8; N Engl J Med 2016;374:1711-22)	$Na+/K+/Ca^2+$ channel and β-receptor antagonist (Class III antiarrhythmic)	First dose: 300 mg IV/IO x 1 Second dose: 150 mg IV/IO x 1 Max: 2.2 g/day	Conflicting data on clinical outcomes compared with lidocaine or placebo for OHCA
Lidocaine (Resuscitation 1997;33:199-205; N Engl J Med 2016;374:1711-22)	Na+ channel antagonist (Class IB antiarrhythmic)	First dose: 1–1.5 mg/kg IV/IO x 1 Subsequent dosing: 0.5–0.75 mg/kg q5–10 min Max 3-mg/kg cumulative dose	Conflicting data on clinical outcomes for OHCA; no improvement in overall or survival to hospital discharge Insufficient evidence to recommend for refractory VF/pVT unless amiodarone unavailable
Magnesium (Clin Cardiol 1993;16:768-74; New Trends Arrhythmias 1991;7:437-42; Circulation 1988;77:392-7)	Stops EAD in torsades de pointes by inhibiting Ca^2+ channel influx	1–2 g diluted in 10 mL of 5% dextrose or sterile water IV/IO × 1	Can aid in stopping torsades de pointes in patients with prolonged QT interval

EAD = early afterdepolarization; ET = endotracheal; IO = intraosseously; IV = intravenously; pVT = pulseless ventricular tachycardia; q = every.

e. Management of PEA/asystole
  i. CPR and treatment of reversible causes are vital to treatment of PEA/asystole.
  ii. Medication therapy
    (a) Epinephrine can be given as soon as feasible (Table 3).
      (1) Stepwise increased mortality is seen if first epinephrine dose is withheld for more than 4 minutes after non-shockable IHCA (BMJ 2014;348:1-9). A randomized, double-blind, placebo-controlled trial found that use of epinephrine in OHCA (around 80% non-shockable rhythms) was associated with greater 30-day survival, but there was no difference in neurologically favorable outcomes because of the severe neurologic impairment of survivors (N Engl J Med 2018;379:711-21).

        (2) Recommended for all non-shockable rhythms to administer epinephrine as soon as feasible (Circulation 2015;132(suppl 2):S315-S367). Data analyses suggest that prompt (less than 5 minutes from non-shockable rhythms administration of epinephrine was associated with greater 1-year survival (Circulation 2018;137:2041-51). These results have been found at both the patient level and the hospital system level (Circulation 2016;134:2105-14). Recent guideline update supports the early usage of epinephrine as soon as feasible in the nonshockable rhythm context (Circulation 2019;140:e881-e894).
    (b) Atropine has been removed from the algorithm because of its lack of therapeutic benefit.

f. Role in treating reversible causes
  i. Echocardiography may be helpful, if available, in the management of PEA to help differentiate the following (Am J Cardiol 1992;70:1056-60):
    (a) Intravascular volume status (ventricular volume).
    (b) Cardiac tamponade.
    (c) Massive pulmonary embolism (right ventricular size, function).
    (d) Mass lesions (tumor, clot).
    (e) Coronary thrombosis (right and left ventricular function, regional wall motion abnormalities).
  ii. Because hypoxia is often a cause of PEA arrest, more focused attention may be given to placement of airway and oxygen delivery.
  iii. See the specific chapters for pulmonary disorders (massive pulmonary embolism and tension pneumothorax), cardiology (acute myocardial infarction and cardiac tamponade), shock (hypovolemic shock), acid-base disorders (acidemia), endocrinologic disorders (hypoglycemia), and electrolytes (hypo/hyperkalemia).

g. Controversial interventions in cardiac arrest
  i. Sodium bicarbonate
    (a) Tissue acidosis and acidemia result during cardiac arrest for several reasons, including inadequate or absent blood flow, arterial hypoxia, or underlying pathophysiology.
    (b) Mainstays of restoring acid-base status include high-quality chest compressions and appropriate ventilation/oxygenation.
    (c) Conflicting evidence exists for the use of sodium bicarbonate, with most data showing no benefit or poor outcome with use (Ann Emerg Med 1998;32:544-53; Resuscitation 1995;29:89-95; Am J Emerg Med 1992;10:4-7; Chest 1990;97:413-9; Resuscitation 1989;17(suppl):S161-172; discussion S199-206; J Emerg Med 2020;59:856-64).
    (d) Data in patients with prolonged CPR efforts (> 20 mins) primarily from VF (~80%) demonstrated an association with increased rate of ROSC (Am J Emerg Med 2016; 34:225-9) after complex retrospective analysis. Caution should be used extrapolating results because significant limitations exist in the study design and all patients included likely were in the metabolic phase of VF (JAMA 2002;288:3035–8) and had pH values < 7.1. A prospective, observational, propensity-matched data suggest that OHCA use of prehospital sodium bicarbonate was associated with a decreased probability of favorable neurologic outcomes and survival (Resuscitation 2017;119;63-9).
    (e) Detrimental effects may be associated with sodium bicarbonate in cardiac arrest, including:
        (1) Compromised coronary perfusion pressure by reducing systemic vascular resistance (JAMA 1991;266:2121-6).
        (2) Shifting the oxyhemoglobin dissociation curve to the left by creating an extracellular alkalosis and decreased release of oxygen.
        (3) Causing hypernatremia and subsequent hyperosmolarity leading to hyperviscosity, potentially impairing blood flow.

        (4) Producing excess CO_2 through rapid dissociation, which can freely diffuse intracellularly (e.g., myocardial and cerebral cells) and cause intracellular acidosis (Science 1985;227:754-6).
        (5) Inactivation of concurrently administered catecholamines (e.g., epinephrine) (Hosp Pharm 1969;4:14-22).
    (f) Certain circumstances may warrant sodium bicarbonate use such as tricyclic antidepressant overdose, bicarbonate (HCO_3-)-wasting causes of metabolic acidosis, and hyperkalemia. In addition, it should be noted that endogenous catecholamines have a blunted response during acidosis which may improve if the acidosis is corrected. Initial dosage should usually be 1 mEq/kg intravenous push with monitoring of clinical status, HCO_3- concentration, laboratory values, and blood gas analysis.
    (g) Recent meta analysis of RCT's found that use of sodium bicarbonate was not superior compared with control in regards to survival and ROSC and may be associated with lower rates of sustained ROSC and good neurological outcome (Int J Emerg Med 2021;14:21).
    (h) A recent RCT in a porcine model of hyperkalemia-induced cardiac arrest discovered that sodium bicarbonate was associated with increased rates of ROSC and reduced time to ROSC (Crit Care Med 2024;52:e67-78). Human investigation may be warranted.

ii. Calcium
    (a) No trial has established any impact on survival in either IHCA or OHCA (Ann Emerg Med 1985;14:626-9; Ann Emerg Med 1985;14:630-2). Recent RCT data in OHCA did not confer benefit of calcium on ROSC (JAMA 2021;326:2268-76).
    (b) Consider in patients with preexisting hypocalcemia and signs and symptoms of acute hypocalcemia (e.g., severe tetany or seizures).
    (c) A recent RCT in a porcine model of hyperkalemia-induced cardiac arrest discovered that calcium chloride was not associated with increased rates of ROSC or time to ROSC (Crit Care Med 2024;52:e67-78).

iii. Atropine
    (a) No prospective studies have evaluated atropine for bradycardic PEA or asystolic cardiac arrest.
    (b) Conflicting results exist from retrospective analyses and case reports (Acta Anaesthesiol Scand 2000;44:48-52; Ann Emerg Med 1984;13:815-7; Ann Emerg Med 1981;10:462-7).
    (c) Atropine has not been associated with harm in treating bradycardic PEA or asystolic cardiac arrest, but because of the lack of convincing evidence of benefit, it is no longer recommended for cardiac arrest but is reserved for symptomatic/life-threatening bradycardia.

iv. Intravenous fluids
    (a) Normothermic, hypertonic, and chilled fluids have been evaluated in animal models and small human studies, with no survival benefit.
    (b) If hypovolemic shock is the suspected cause of the cardiac arrest, fluid resuscitation should be initiated immediately.

v. For indications of fibrinolysis for cardiac arrest, see the Pulmonary chapter for treatment of pulmonary embolism and the Cardiology chapter for treatment of acute myocardial infarction.

vi. Pacing
    (a) Transcutaneous, transvenous, and transmyocardial pacing is not beneficial in cardiac arrest and does not improve ROSC or survival.
    (b) Not recommended for routine use in cardiac arrest.

vii. Dextrose
    (a) Animal data has demonstrated that dextrose administration before, during, or after cardiac arrest leads to higher rates of mortality and worse neurological outcomes (J Crit Care. 1987;2:4–14; Surgery 1990;72:1005–11; Acta Anaesthesiol 1986;100:505–11).

(b) Human retrospective data from IHCA demonstrated that dextrose administration during resuscitation was associated with a significantly decreased chance of survival to discharge and good neurological outcome (Crit Care 2015;19:160[1-8]).

viii. Cyclosporine - A randomized, single-blind trial found no impact on target organ damage, survival, or favorable neurologic function, contrary to experimental evidence (JAMA Cardiol 2016;1:557-65).

h. For information on acute symptomatic arrhythmias (bradycardias and tachycardias), see the Cardiovascular Critical Care I chapter.

D. Post–Cardiac Arrest Care and Recovery (IHCA and OHCA - chain of survival): Objectives of post–cardiac arrest care can be divided into initial (stabilization phase) and subsequent (continued management and additional emergent activities) (Circulation 2010;122:S768-786; Circulation 2008;118:2452-83; Circulation 2020;142:S366-S468).

1. Initial
   a. Optimize hemodynamics: Target MAP 65–100 mm Hg, central venous pressure 8–12 mm Hg, central venous oxygen saturation greater than 70%, urine output greater than 1 mL/kg/hour, and normal serum lactate.
      i. Consider the patient's normal BP, cause of arrest, and severity of myocardial dysfunction for all values above. Recent study has found that lower MAP goals (63 mm Hg vs. 77 mm Hg) did not portend worse survival or neurologic outcomes (N Engl J Med 2022;387:1456-66).
      ii. Use intravenous crystalloids and colloids, continuous vasopressors and inotropes, transfusions, and renal replacement as needed to meet target goals.
      iii. In a randomized study of vasopressor dependent shock post-cardiac arrest, the provision of corticosteroids (hydrocortisone 100 mg intravenously every 8 hours x 7 days or until shock reversal) did not improve time to shock reversal, rate of shock reversal, or clinical outcomes (Crit Care 2016;20:821-8]) and thus should be avoided unless otherwise indicated.
   b. Transfer patient to a system (OHCA) or unit (IHCA) that can provide advanced post–cardiac arrest care, including continuous electrocardiographic (ECG) monitoring with immediate 12-lead ECG, central intravenous access if possible, coronary reperfusion, and/or temperature control (i.e., targeted temperature management).
   c. Try to identify and treat the reversible causes of cardiac arrest (Table 2). Laboratory and diagnostic tests should be performed to aid in identifying a potential underlying cause.
2. Continued management and additional emergency activities
   a. Consider body temperature regulation. Should be considered for any patient with ROSC who does not follow commands (i.e., comatose) after cardiac arrest.
      i. The terminology "temperature control" that encompass the practices of hypothermia, normothermia, and fever prevention, has replaced the previous "targeted temperature management" terminology (Perman 2024).

ii. Early evidence suggested significant benefit for primarily shockable (VF/pVT) OHCA (N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; Circulation 2010;122:S768-786). A meta-analysis demonstrated a similar nonsignificant reduction in mortality and poor neurological outcome (Am J Med 2016;129:522-527) when including all randomized studies. After exclusion of one trial that allowed for temperature control in the control arm, there was a significant reduction in poor neurological outcome when implementing temperature control. A Cochrane analysis found that conventional temperature control compared with no temperature control conferred the benefit of favorable neurological outcome and survival with only a slight increase in the incidence of pneumonia and hypokalemia (Cochrane Database Syst Rev 2016;2:CD004128). The Targeted Temperature Management 2 (TTM2) study, published in 2021 comparing goal temperature of 33°C with normothermia (N Engl J Med 2021;384:2283-94), found similar outcomes surrounding neurologic function and overall survival. This has led some to advocate for normothermia (i.e., avoidance of fevers) versus hypothermia. In addition, in the TTM2 study, patients who underwent therapeutic hypothermia had more adverse events.

iii. Evidence for nonshockable rhythms IHCA and OHCA has conferred results similar to those in early studies of shockable rhythms demonstrating increased survival and better neurological outcomes (N Engl J Med 2019;381:2327-37; Circulation 2015;132:2146-51).

iv. Optimal targets, timing, duration, and other variables still unclear:
   (a) Goal target body temperature 32°C–37.5°C given data showing that targeting 36°C instead of 33°C may be equivocal (Circulation 2015;132(suppl 2):S315-S367; N Engl J Med 2013;369:2197-206; N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; Circulation 2024;149:e254-73). Additional investigations have found that targeting a warmer temperature (36°C) may lead to reduced times in goal temperature range but with increased fever rates (Resuscitation 2017;113:39-43). Similar results have been found in other studies (Crit Care Med 2020;48:362-9; Resuscitation 2019;143:142-7). The TTM2 study, as mentioned earlier, has led some to consider strict avoidance of hyperthermia, using active maintenance of normothermia instead of targeting hypothermic temperature goals (N Engl J Med 2021;384:2283-94). European guidelines suggest a more modest application of literature and suggest avoiding fever while continuously monitoring core temperature (Intensive Care Med 2022;48:261-9).
   (b) Duration of at least 12 hours; optimally, a minimum of 24 hours. A 48-hour duration did not seem to confer any benefit compared with a 24-hour duration in a multicenter randomized study (JAMA 2017;318:341-50). Multiple studies are ongoing investigating the optimal duration of temperature control.
   (c) Initiate temperature control as soon as possible (within 2 hours, if possible), with goal temperature attainment within 6–8 hours; however, several retrospective studies have not confirmed the timing of initiation or the timing of temperature attainment as predictors of neurologic outcome (Acta Anaesthesiol Scand 2009;53:962-34; Int J Cardiol 2009; 133:223-8). Intra-arrest temperature control is currently being investigated, but human data is limited. Prehospital infusion of cold intravenous fluids for OHCA in several randomized controlled studies conferred no benefit and may increase the number of complications; thus, it is not recommended (Circulation 2015;132(suppl 2):S315-S367; Circulation 2016;134:797-805).
   (d) Modality for cooling includes feedback-controlled endovascular systems, surface-cooling devices, ice packs/bags, cooling blankets, iced isotonic fluids, and/or extracorporeal membrane oxygenation.

(e) Axillary or oral temperature monitoring is inadequate for temperature control (Acta Anaesthesiol Scand 1998;42:1222-6; J Cardiothorac Vasc Anesth 1996;10:336-41), which requires central/core temperatures by esophageal, bladder (avoid in anuric patients), or pulmonary artery temperature monitoring. Ideally, the monitoring modality chosen will be used for other indications as well.

v. The major complications of temperature control are related to the physiologic and adaptive responses to the temperature-changing process of temperature control (Table 4). The adverse events of sepsis, myoclonus, seizures, and hypoglycemia within 72 hours of temperature control have been associated with poor neurologic outcome (Crit Care 2015;19:283-96).

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia

Musculoskeletal (Crit Care Med 2015;43:2228-38; N Engl J Med 2013;369:2197-206; Anesthesiology 2009;111:110-5; Br J Anaesth 2005;94:756-62; N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; JAMA 1997;277:1127-34; Am J Physiol 1960;198:481-6)	**Shivering:** Body's natural response to hypothermia, preceded by arteriovenous vasoconstriction; most common complication of hypothermia; can increase metabolic heat production by 600%, thereby slowing the induction of hypothermia. Typically slows or stops at core temperatures < 33.5°C 1. Agents that decrease the shivering threshold (i.e., decreases the temperature at which shivering will occur): a) Scheduled acetaminophen 650 mg q4–6 hr or buspirone 30 mg q12 hr reduces the shivering threshold by 0.2ºC–0.4ºC b) Magnesium sulfate reduces the shivering threshold by ~0.3°C c) Meperidine decreases the shivering threshold by up to 2°C but should be avoided because of decreased effective glomerular filtration rate (GFR) during hypothermia and increased risk of seizures when meperidine is used in patients with decreased GFR d) Dexmedetomidine and clonidine decrease the shivering threshold by ~0.8°C, but extreme caution should be used because of the hypotensive and bradycardic effects of both agents e) Propofol decreases the shivering threshold by ~0.6°C and has a linear relationship between serum concentrations and reduction in body temperature; caution should be used, given the hypotensive and bradycardic effects 2. Options to stop shivering include: a) Continuous or as-needed paralytics can be used for prevention and treatment of shivering (see the chapter on management of paralytics for appropriate selection and dosing of agent[s]) —Hypothermia decreases clearance and prolongs the duration of neuromuscular blockade (see Table 5 for examples) —Train of four is not a reliable method of monitoring during hypothermia; clinical monitoring or continuous EEG (electroencephalography) may be warranted b) Surface warming if using internal cooling devices c) Chilled fluids to promote faster core temperature reduction

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia *(continued)*

Neurologic (Circulation 2010;122:S729-767; Circulation 2008;118:2452-83; Pharmacotherapy 2008;28:102-11; Ther Hypothermia Temp Manag 2016;6:189-93)	**Sedation and Analgesia:** Adequate pain control and sedation must be used Target Richmond Agitation and Sedation Scale score of -3 to -5 (see chapter on sedation for agent selection and dosing) during hypothermia Accumulation of parent and active metabolites can be expected for each analgesic and sedative, which leads to prolonged sedation and potentially untoward adverse effects (see Table 5 for examples) **Seizures:** Possible complication of cardiac arrest and therapeutic hypothermia Consider benzodiazepines as first line to abort seizure Phenytoin, barbiturates, valproic acid, and propofol can all be used, with vigilant monitoring of adverse effects because of decreased clearance (see Table 5 for examples; for dosing and monitoring values, see the Status Epilepticus section in the Neurocritical Care chapter) **Intracranial Pressure:** Increases post-cardiac arrest likely because of ischemic injury and cytotoxic edema and is partially attenuated by temperature control Major increase appears to occur during rewarming phase of temperature control Uncertain if targeted reduction therapy would impact outcomes
Cardiac (Heart Lung 2001;30:161-3; Int Anesthesiol Clin 1964;2:803-27)	**Arrhythmias:** Include VT, VF, and atrial fibrillation If life threatening, should consider discontinuing therapeutic hypothermia and active rewarming Sinus bradycardia is common during cooling and, in isolation, should not be treated unless it leads to hemodynamic instability (e.g., hypotension or organ dysfunction) **ECG observations:** Prolonged PR, QRS, and QT intervals Caution should be exercised when using medications that prolong the QT interval **Hemodynamics:** Decreased cardiac output Fluid shifts away from central compartment Vasoconstriction during cooling, which may lead to increased blood pressure Vasodilation during rewarming, which may lead to decreased blood pressure
Hepatobiliary (Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;23:192-7; Anesthesiology 2000;92:84-93; Clin Pharmacol Ther 1979;25:1-7)	Elevated transaminases Reduced activity of non-cytochrome and cytochrome P450–mediated metabolism See Table 5 for examples of metabolic changes in selected medications during hypothermia

Table 4. Major Organ-Specific Complications of Therapeutic Hypothermia *(continued)*

Endocrinologic (N Engl J Med 2002;346:557-63; Endocrinology 1970;87:750-5)	Hyperglycemia caused by decreased insulin production and effect in periphery, increased gluconeogenesis, and glycogenolysis Continuous insulin infusions may be necessary for glucose control. Goal should be < 180 mg/dL without inducing hypoglycemia
Renal (Resuscitation 2004;60:253-61; J Neurosurg 2001;94:697-705)	Decreased effective glomerular filtration (urine output may increase because of cold diuresis, but not effective clearance) Electrolyte shifts (K+, PO_4^{3}-, Na+, Ca^{2}+) during cooling phase; reverse upon rewarming, thus caution should be exerted with replacement
Hematologic (Pharmacotherapy 2008;28:102-11; Br J Haematol 1999;104:64-8; Crit Care Med 1992;20:1402-5)	Coagulopathy caused by thrombocytopenia, impaired activation and activity of clotting factors, impaired platelet function Actively bleeding patients should not be cooled

Table 5. Pharmacokinetic and Pharmacodynamic Changes of Selected Medications During Hypothermia

Fentanyl	Plasma concentration increases by 25% with a 3.7-fold decrease in clearance
Morphine	Receptor affinity (μ) decreases as temperature decreases
Propofol	Plasma concentration increases by 28%; decreased clearance
Midazolam	Clearance decreases by about 11% per degree below 36.5°C
Rocuronium	Clearance decreases by 50%, increases duration of action 2-fold
Vecuronium	Clearance decreases by 11% per degree Celsius; increases duration of action 2-fold
Cisatracurium	Eliminated by Hofmann elimination, which is a temperature-dependent enzymatic process; anticipate prolonged activity
Phenytoin	AUC (area under the concentration-time curve) increases by 180%; clearance and elimination rate constant decrease by 50%

Information from: Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;233:192-7; Anesthesiology 2000;92:84-93; Br J Haematol 1999;104:68-8; Eur J Anaesthesiol Suppl 1995;1:95-106; Clin Pharmacol Ther 1979;25:1-7)

        vi. Rewarming should be a passive process (around 0.33°C–0.5°C per hour) (Acta Anaesthesiol Scand 2009;53:926-34; N Engl J Med 2002;346:557-63; N Engl J Med 2002;346:549-56). Rapid rewarming can cause extreme electrolyte shifts and vasodilation with associated hypotension.
        vii. Though the exact temperature goals and duration of temperature control is still being investigated, avoidance of fever and hyperthermia is clear and should be maintained during the first 48–72 hours after cardiac arrest (Arch Intern Med 2001;161:2007-12; Resuscitation 2013;84:1062-7; J Crit Care 2017;38:78-83; Intensive Care Med 2022;48:261-9).
    b. Identify and treat acute coronary syndromes.
        i. Cardiovascular disease and acute coronary ischemia are the most common causes of cardiac arrest (Am Heart J 2009;157:312-8; N Engl J Med 1997;336:1629-33).
        ii. Consideration of treatment of acute coronary syndromes should not be deferred in patients who are comatose or when temperature control is used.

iii. Emergent coronary angiography is no longer recommended over a delayed/selective strategy in patients with ROSC after cardiac arrest. Exceptions exist for patients with ST-segment–elevation myocardial infarction, shock, electrical instability, signs of significant myocardial damage, or ongoing ischemia (Circulation 2024;149:e254-73). An analysis suggests that risk stratification and admission prognosis can help determine which patients will benefit from angiography (JACC Cardiovasc Interv 2018;11:249-56).

iv. Effects of antiplatelet and antithrombotic drugs augmented by derangements in normal platelet activation/coagulation pathways caused by hypothermia.

v. See the Cardiology chapter for the workup and treatment of acute coronary syndromes.

c. Optimize mechanical ventilation.

i. Goal arterial oxygen saturation is 94% or greater. A recent study found equivocal results with restrictive (Pao2 target of 68–75 mm Hg) versus liberal (Pao2 target of 98–105 mm Hg) oxygenation targets in comatose survivors of OHCA (N Engl J Med 2022;387:1456-66).

ii. Avoid hyperventilation or over-bagging to avoid increase in intrathoracic pressure and decrease in cardiac output.

iii. Goal $\mathrm{Pa_{CO_2}}$ is 40–45 mm Hg or $\mathrm{P_{ETCO_2}}$ 35–40 mm Hg.

d. Support organ systems

i. Vasopressor/inotropes to support end-organ perfusion (see Table 6)

(a) Adrenergic medications should not be administered with alkaline solutions or sodium bicarbonate because they are inactivated (Hosp Pharm 1969;4:14-22).

(b) Central line is recommended because any agent with α-agonist properties can lead to extravasation and tissue necrosis.

Table 6. Common Vasoactive Agents Used After Cardiac Arrest

Medication	Typical Dosing Range (mcg/kg/min)	Clinical Pearls
Epinephrine	0.03–0.3	Mixed α and $\beta_{(1>2)}$ activity Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Used for symptomatic bradycardia Used for hemodynamically unstable anaphylactic reactions Higher doses associated with increased α_1 activity
Norepinephrine	0.03–0.3	α > $\beta_{(1>2)}$ receptor activity Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Should be used in volume-resuscitated patients First line for septic shock Higher doses associated with increased α_1 activity
Phenylephrine	0.3–3	Pure α-agonist Used to treat severe hypotension (e.g., SBP < 70 mm Hg) Should be used in volume-resuscitated patients Avoid in patients with low cardiac output

Table 6. Common Vasoactive Agents Used After Cardiac Arrest *(continued)*

Medication	Typical Dosing Range (mcg/kg/min)	Clinical Pearls
Dopamine	2–20	In general, dose-related receptor activity: 2–5 mcg/kg/min dopamine receptor, 5–10 mcg/kg/min β_1-receptor, > 10 mcg/kg/min α_1-receptor Does not provide exclusive receptor activity across dosing ranges and, thus, can be arrhythmogenic at any dose Use cautiously in patients with a history of heart disease or arrhythmias Useful for patients with bradycardia and hypotension
Dobutamine	2–20	Predominance of inotropic properties but with activity on $\beta_1 > \beta_2 > \alpha_1$-receptor Used to treat low cardiac output α_1-agonist and β_2-agonist counterbalance, leading to little change in systemic vascular resistance Can lead to vasodilation in select patients Less systemic or pulmonary vasodilation than milrinone More tachycardia than milrinone but similar risk of ventricular arrhythmias Use cautiously in patients with a history of arrhythmias
Milrinone	0.25–0.75	Phosphodiesterase type 3 inhibitor leading to increased intracellular cAMP leading to influx of calcium and subsequently inotropy and chronotropy Used to treat low cardiac output Loading dose rarely used because of significant systemic hypotension Longer duration of activity than dobutamine Accumulates in renal dysfunction More systemic and pulmonary vasodilation than dobutamine Less tachycardia than dobutamine but similar risk of ventricular arrhythmias Use cautiously in patients with a history of arrhythmias

[a] See chapter on shock for a detailed discussion regarding selection of agent, dosing, pharmacology, and clinical considerations.
SBP = systolic blood pressure

ii. Glucose management (Circulation 2010;122:S768-786; Circulation 2008;118:2452-83)
    (a) Avoidance of severe hypoglycemia (40 mg/dL or less)
    (b) Target moderate glucose control: 144–180 mg/dL
    (c) May require continuous insulin infusion to maintain goals

iii. Seizure control/prevention (Neurology 1988;38:401-5; JAMA 1985;253:1420-6): Myoclonus and seizures, or both, can occur in up to 35% of adult patients who achieve ROSC and are more common in those who remain comatose. Electrographic patterns seen in the patient population include electrographic seizures, status epilepticus, and ictal-interictal continuum patterns (Circulation 2024;149:e254-73).
    (a) Clonazepam, valproic acid, and levetiracetam are all effective for myoclonus, but clonazepam should be considered first line.
    (b) Benzodiazepines, phenytoin, valproic acid, propofol, and barbiturates are all effective for post–cardiac arrest seizures. Seizures and status epilepticus are treated similarly to non-cardiac arrest populations. For dosing and monitoring guidelines, see the Status Epilepticus section of the Neurocritical Care chapter.

      - (c) For patients with ictal-interictal continuum patterns on electroencephalography can be given nonsedating antiseizure medications (i.e., non-benzodiazepine).
    - iv. Renal dysfunction: The indications for initiating renal replacement therapy in cardiac arrest survivors are the same as in critically ill patients in general (Lancet 2005;365:417-30).
    - v. Infectious disease: Association has been shown between the use of prophylactic antibiotics and decreased incidence of pneumonia and sepsis (Resuscitation 2015;92:154-9) in patients who underwent temperature control to goal 32-34°C. Impact on length of stay or neurological outcome was not demonstrated and no information is available regarding impact of higher temperature goals on the above outcomes.
- e. Assess prognosis.
    - i. Brain injury and cardiovascular instability are the main determinants of survival after cardiac arrest (Intensive Care Med 2004;30:2126-8).
    - ii. If temperature control is used, a delay of 72 hours after rewarming should be implemented for prognostication.
    - iii. If temperature control is not considered:
        - (a) Prognostication should wait until 72 hours after ROSC.
        - (b) No clinical neurologic sign has shown to be predictive of neurologic prognosis less than 24 hours after arrest (Neurology 2006;66:62-8; Crit Care Med 1987;15:820-5).
    - iv. Prudent to perform any prognostication after removal of opioids, sedatives, paralytics, and so forth.
    - v. Using several modalities of testing including clinical examination, neurophysiological testing, and imaging is recommended.
- f. Recovery – Care and support during recovery (Circulation 2020;142(16_suppl_2):S366-468)
    - i. Assist survivors with rehabilitation needs. Multimodal rehabilitation assessment and treatment of physical, neurologic, cardiopulmonary, and cognitive impairments are recommended before hospital discharge.
    - ii. Cardiac arrest survivors and their caregivers are recommended to receive comprehensive, multidisciplinary discharge planning, including medical and rehabilitative treatment recommendations, and to return to activity/work expectations.
    - iii. Structured assessment for anxiety, depression, posttraumatic stress, and fatigue is recommended for cardiac arrest survivors and their caregivers.
    - iv. New recommendations also call for provider debriefing and referral for emotional support, when needed, for those responding to and participating in resuscitation efforts.

Patient Case

6. K.G., a 71-year-old woman with a history of atrial fibrillation, coronary artery disease status post three-vessel coronary bypass artery grafting 6 years ago, diabetes, and osteoarthritis, is being admitted to your MICU for temperature control after PEA arrest and subsequent ROSC. K.G., who remained comatose after the ROSC, was intubated and is now hemodynamically stable (BP 94/72 mm Hg and HR 86 beats/minute). Which is the most accurate statement regarding temperature control?
   - A. Hypoglycemia is a common complication of hypothermia and may require continuous dextrose infusions.
   - B. Dose modifications or avoidance of cytochrome P450 (CYP)–metabolized medications should occur during hypothermia.
   - C. The optimal duration of temperature control should be at least 72 hours to affect survival.
   - D. Temperature targets should be 28°C–30°C to improve the neurologic recovery.

II. HYPERTENSIVE CRISIS

A. Definitions have been recently revised to capture the importance of blood pressure-related organ damage (Bress 2024; Johnson 2012; Marik 2007; Aggarwal 2006):
   1. Asymptomatic, markedly elevated blood pressure: A systolic blood pressure (SBP) greater than 180 mm Hg and/or a diastolic blood pressure (DBP) greater than 110–120 mm Hg without evidence of new or worsening target organ damage
   2. Hypertensive emergency: An SBP greater than 180 mm Hg and/or DBP greater than 110–120 mm Hg with new or worsening target organ dysfunction (e.g., acute kidney injury, heart failure exacerbation, obtundation). Table 7 lists example conditions that, when accompanied by high BP, define hypertensive emergency
      a. Importantly, target organ damage may still occur below SBP and DBP thresholds used in definitions.
   3. MAP: Average pressure in the arteries (mm Hg) experienced during one cardiac cycle. Calculated by MAP = 1/3 SBP + 2/3 DBP.

Table 7. Examples of Acute Target Organ Damage and Clinical Presentations

Eclampsia, preeclampsia	Hypertensive encephalopathy
Acute kidney injury	Acute shortness of breath, flash pulmonary edema, or acute left ventricular dysfunction
Acute aortic dissection (type A or B)	Acute intracranial bleeding (nontraumatic)
Seizures	Acute myocardial ischemia/infarction
Retinopathy	Cerebral infarction

B. Estimated that 1-3% of patients with hypertension will experience a hypertensive crisis (Acta Med Scand Suppl 1981;650:1-62; Am J Cardiol 2011;108:1277-82),

C. 10-year survival approaches 70% (Q J Med 1993;96:485-93), with 1-year survival greater than 90%.

D. Common Causes (Cardiol Clin 2012;30:533-43; Cardiol Clin 2006;24:135-46):
   1. Intoxications – Cocaine, amphetamines, phencyclidine hydrochloride, stimulant diet pills
   2. Nonadherence to antihypertensive regimen

3. Withdrawal syndromes (e.g., clonidine or β-antagonists)
4. Drug-drug/drug-food interactions (e.g., monoamine oxidase inhibitors and tricyclic antidepressants, antihistamines, or tyramine)
5. Spinal cord disorders
6. Pheochromocytoma
7. Pregnancy

E. Management:
   1. Asymptomatic, markedly elevated blood pressure: Repeat BP measurement using proper technique to confirm result. Address underlying acute conditions that may be contributory (e.g., pain, anxiety, etc.). If chronic hypertension is present, it may be reasonable to resume with or without intensification of home antihypertensive program. Over-agressive treatment may occur if not appropriately differentiated from hypertensive emergency.
   2. Hypertensive emergency: Requires ICU monitoring and intravenous medications. See goals listed in Table 8.

Table 8. Time Interval for BP Lowering with Hypertensive Emergency[a]

Goal Time	BP Target
< 60 min	↓ DBP by 10%–15% or MAP by 25% with goal DBP ≥ 100 mm Hg
2–6 hr	SBP 160 mm Hg and/or DBP 100–110 mm Hg
6–24 hr	Keep above BP goals (hours 2–6) during first 24 hr
24–48 hr	Outpatient BP targets

[a]See compelling conditions in the text that follows.

a. A 25% reduction in MAP during the first hour is targeted to maintain cerebral perfusion (blood flow autoregulation) and to not precipitate ischemia, which has been found with >50% reductions (Stroke 1984;15:413-6).
b. If neurologic function deteriorates during the initial 25% decrease (or during subsequent lowering), therapy should be discontinued or a reduced percent decrease should be targeted (N Engl J Med 1990;323:1177-83).
c. Compelling conditions leading to unique treatment timing and goals:
   i. Acute aortic dissection
      (a) Propagation of acute aortic dissection is dependent on arterial BP and shear stress (force of left ventricular contraction as a function of time).
      (b) HR and contractility control can minimize shear stress and, together with BP, become a target of management.
      (c) Goal HR less than 60 beats/minute and SBP less than 100 mm Hg as soon as possible (within 5–10 minutes).
   ii. Acute ischemic stroke
      (a) Hypertension with ischemic stroke is an adaptive response to maintain cerebral perfusion pressure to the brain.
      (b) Cerebral perfusion pressure (CPP) equals mean arterial pressure minus intracranial pressure (ICP): CPP = MAP – ICP.

(c) Treatment should occur only if (1) thrombolytic therapy is required (goal SBP less than 185 mm Hg and DBP less than 110 mm Hg before thrombolysis initiation - has been shown to decrease risk of bleeding), (2) other target organ damage occurs, or (3) SBP is greater than 220 mm Hg and/or DBP is greater than 120 mm Hg (Stroke 2013; 44: 870-947).

(d) If treatment in indicated (outside of thrombolytic goal stated above): goal 10%–20% MAP reduction over 24 hours (Cardiol Clin 2012;30:533-43; CNS Drugs 2015; 29: 17-28).

iii. Intracerebral hemorrhage

(a) BP reduction goals will be based on individual factors, including medical history; ICP, if known; demographics such as age; presumed cause of hemorrhage (e.g., arteriovenous malformation); and interval since onset.

(b) High BP is associated with worse outcomes, including hematoma expansion, neurological deterioration, death, and inability to perform activities of daily living after intracranial hemorrhage (Eur J Neurol 2013;20:1277-83; Stroke 2013;44:1846-51; J Hypertens 2008;26:1446-52).

(c) BP reductions in patients without ICP elevations to goal SBP targets of less than 140 mm Hg and/or less than 160 mm Hg have been shown to be safe and may confer benefit regarding functional recovery (Stroke 2013;44:1846-51; Stroke 2012;43:2236-8; Arch Neurol 2010;67:570-6; Hypertension 2010;56:852-8; Lancet Neurol 2008;7:391-9; N Engl J Med 2013; 368: 2355-2365). In a study evaluating an early (within 6 hours) intensive care bundle that included the early intensive lowering of systolic blood pressure (target less than 140 mm Hg), strict glucose control in those without diabetes, antipyrexia treatment (target body temperature less than or equal to 37.5°C), and rapid reversal of warfarin-related anticoagulation (target international normalized ratio less than 1.5) within 1 hour, patients had improved functional outcomes and fever adverse events (Lancet 2023;402:27-40). Although promising, given the bundled nature of the intervention, it is hard to know what portion of the care bundle was driving the benefits seen.

(d) It is unclear whether aggressive targets are safe in patients with extreme elevations in BP (i.e., SBP greater than 220 mm Hg), patients with large hematomas, or those with elevations in ICP. Aggressive therapy can be considered, though a more modest reduction to an SBP less than 180 mm Hg or a MAP less than 130 mm Hg over the first 24 hours is recommended (Stroke 2015;46:2032-60).

3. Agents for BP management of hypertensive emergency

a. The drugs of choice for many presentations of hypertensive emergency are intravenous nicardipine or nitroprusside (Neurology 2014;83:1523-9; Curr Hypertens Rep 2014;16:450; High Blood Press Cardiovasc Prev 2022;29:33; Hypertension 2020;75:1334-57).

i. Intravenous nitroprusside works rapidly and is safe in the presence of renal and/or hepatic impairment for short-term use (24 hours or less).

ii. Continuous BP monitoring (e.g., arterial line) is recommended with use because rapid changes can occur.

iii. Nitroprusside can increase ICP and may result in coronary steal; caution or avoidance should be considered in patients with elevated ICP and acute myocardial ischemia/infarction.

b. Table 9 summarizes available agents, dosing, onset, duration, and hemodynamic considerations. Table 10 summarizes possible indications and special considerations.

Table 9. Medications Used in Hypertensive Emergencies

Medication	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
Nitroprusside	IV 0.25–10 mcg/kg/min Titrate by 0.1–0.2 mcg/kg/min q5 min	Seconds	1–2 min	↓	↓↓	↑
Hydralazine	IV bolus: 10–20 mg q30 min PRN	IV: 10 min	IV: 1–4 hr	↔	↓	↑
Nicardipine	IV 5–15 mg/hr Titrate by 2.5 mg/hr q5–10 min	5–10 min	2–6 hr	↔	↓	↑
Clevidipine	IV 1–6 mg/hr Titrate by 1–2 mg/hr q90s or consider doubling the dose every 90 seconds Consider max 21 mg/hr averaged over 24 hr	1–4 min	5–15 min	↔	↓	↑
Nitroglycerin	IV 5–200 mcg/min Titrate by 5–25 mcg/min q5–10 min	2–5 min	5–10 min	↓↓	↓↔	↔↑
Esmolol	IV 25–300 mcg/kg/min (bolus of 500 mcg/kg, not often required given short onset) Titrate by 25 mcg/kg/min q3–5 min	1–2 min	10–20 min	↔	↔	↓
Metoprolol	IV bolus: 5–15 mg q5–15 min PRN	5–20 min	2–6 hr	↔	↔	↓
Labetalol	IV bolus: 20 mg, may repeat escalating doses of 20–80 mg q5–10 min PRN IV 1–2 mg/min Titrate by 1–2 mg/min q2 hr given longer half-life	2–5 min, peak 5–15 min	2–6 hr	↔	↓	↓
Enalaprilat	IV bolus: 1.25 mg q6 hr Titrate no more than q12–24 hr; max dose 5 mg q6 hr	15–30 min	12–24 hr	↓	↓	↑
Phentolamine	IV bolus: 1–5 mg PRN	Seconds	15 min	↔	↓	↑
Fenoldopam	IV 0.03–1.6 mcg/kg/min Titrate by 0.05–1 mcg/kg/min q15 min	10–15 min	10–15 min	↔↓	↓	↑

IM = intramuscular; IV = intravenous; PRN = as needed.

Table 10. Indications and Special Considerations for Medications Used for Hypertensive Emergencies

Medication	Indication	Special Consideration
Nitroprusside	Most indications (exclusions: ICP elevation, coronary infarction/ischemia)	Liver failure – cyanide accumulation Renal failure – thiocyanate accumulation Can draw serum cyanide and thiocyanate concentrations to monitor Toxicity associated with prolonged infusions (> 72 hr) or high doses (> 3 mcg/kg/min) May result in coronary steal Increases ICP
Hydralazine	Pregnancy	Can result in prolonged hypotension (less predictable dose response) Risk of reflex tachycardia Headaches, lupus-like syndrome (with long-term use)
Nicardipine	Most indications, especially acute ischemic or hemorrhagic stroke	Risk of reflex tachycardia Infusion can lead to large fluid volumes administered
Clevidipine	Most indications, especially acute ischemic or hemorrhagic stroke	Formulated in oil-in-water formulation providing 2 kcal/mL of lipid calories Caution for patients allergic to soy or eggs
Nitroglycerin	Coronary ischemia/ infarction Acute left ventricular failure Pulmonary edema	Tachyphylaxis occurs rapidly, requiring dose titrations Adverse effects: Flushing, headache, erythema; often dose-limiting adverse effects Veno > arterial vasodilator
Esmolol	Aortic dissection Coronary ischemia/ infarction	Contraindicated in acute decompensated heart failure, bradycardia Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate esmolol first because of the delayed onset relative to vasodilators such as nitroprusside) Metabolism is organ-independent (hydrolyzed by esterases in blood) Useful in tachyarrhythmias
Metoprolol	Aortic dissection Coronary ischemia/ infarction	Contraindicated in acute decompensated heart failure, bradycardia, heart block Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate metoprolol first because of the delayed onset relative to vasodilators such as nitroprusside) Useful in tachyarrhythmias
Labetalol	Aortic dissection Coronary ischemia/ infarction Pregnancy	May be used as monotherapy in acute aortic dissection Contraindicated in acute decompensated heart failure, reactive airway disease Prolonged hypotension and/or bradycardia may be experienced with overtreatment; dose cautiously

Table 10. Indications and Special Considerations for Medications Used for Hypertensive Emergencies *(continued)*

Medication	Indication	Special Consideration
Enalaprilat	Acute left ventricular failure	Contraindicated in pregnancy acute myocardial infarction, unstented bilateral renal artery stenosis Caution in dose adjustments given slow onset and prolonged duration of action
Phentolamine	Catecholamine excess (e.g., pheochromocytoma)	Use in catecholamine-induced hypertensive emergency
Fenoldopam	Most indications	Risk of reflex tachycardia Caution with glaucoma, sulfite sensitivity Can cause hypokalemia, flushing May increase ICP

ICP = intracranial pressure.

c. Certain populations require specific medication therapy approaches:
   i. Pregnancy
      (a) Definitions of hypertensive disorders in pregnancy (Obstet Gynecol 2013;122:1122-31; Obstet Gynecol 2019;133:e26-50; Obstet Gynecol 2020;135:1492-5):
         (1) Hypertension in pregnancy: SBP greater than or equal to 140 mm Hg or DBP greater than or equal to 90 mm Hg, or both, measured on two occasions at least 4 hours apart
         (2) Gestational hypertension: SBP greater than or equal to 140 mm Hg or DBP greater than or equal to 90 mm Hg, or both, measured on two occasions at least 4 hours apart diagnosed after 20 weeks of gestation and a previously normal BP
         (3) Severe-range hypertension: SBP greater than or equal to 160 mm Hg or DBP greater than or equal to 110 mm Hg, or both, measured on two occasions at least 4 hours apart
         (4) Preeclampsia: Gestational hypertension or severe-range hypertension, in addition to at least 1 of the following:
            (A) Proteinuria (greater than or equal to 300 mg/24-hour urine, or protein:creatinine greater than or equal to 0.3, or dipstick 2+ only if other quantitative methods not available)
            (B) Renal insufficiency (serum creatinine greater than 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease)
            (C) Thrombocytopenia (greater than 100 ×109/L)
            (D) Impaired liver function (ALT/AST greater than or equal to two times upper limit of normal)
            (E) Pulmonary edema
            (F) New-onset headache or visual disturbances (not caused by alternative diagnoses)
         (5) Preeclampsia with severe features: Severe-range hypertension and:
            (A) Renal insufficiency
            (B) Thrombocytopenia
            (C) Impaired liver function
            (D) Severe persistent right upper quadrant or epigastric pain unresponsive to medications
            (E) Pulmonary edema
            (F) New-onset headache or visual disturbances

(6) Eclampsia: new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions often associated (but not required) with hypertension in pregnancy

(b) Preeclampsia with severe features can only be managed by delivery of the baby.

(c) Magnesium can be considered as an adjunctive therapy to decrease seizure risk or if seizures develop.

(d) Intravenous medications should only be considered for (1) severe-range hypertension, (2) preeclampsia/eclampsia, and/or (3) hypertensive emergency (signs of target organ damage) in a pregnant patient.

(e) Hydralazine and labetalol are feasible first-line options, and labetalol may have fewer adverse effects (Am J Health Syst Pharm 2009;66:337-44). Choice of agent should be dependent on provider familarity and local practices and protocols (Cochrane Database Syst Rev 2013;2013:CD001449).

(f) BP target goal for severely elevated BPs, preeclampsia/eclampsia, and hypertensive emergency in a pregnant patient is 160/110 mm Hg or less with avoidance of abrupt decreases in BP, which can lead to potentially harmful fetal effects. Because of this caution, the MAP should be decreased by ~20%-25% over the first few minutes to hours, and the BP should then be further decreased to the target of 160/110 mm Hg or less over the subsequent hours.

ii. Catecholamine-induced hypertensive emergency

(a) Phentolamine is the drug of choice because it competitively inhibits α-adrenergic receptors.

(b) β-Selective antagonists are contraindicated unless the patient is fully α-blocked.

iii. Cocaine-induced hypertensive emergency (Ann Emerg Med 2008;52:S18-20; Chest 2007;131:1949-62)

(a) Benzodiazepines are used to target the central effects of cocaine as first-line therapy and often will result in control of tachycardia and hypertension. Can consider diazepam 5–10 mg intravenously or lorazepam 2–4 mg intravenously titrated to effect.

(b) If central control of cocaine-induced hypertension fails, consider direct α-antagonism with phentolamine.

(1) Phentolamine 1 mg intravenously; repeat every 5 minutes as needed.

(2) If direct α-antagonism does not gain control or is unavailable, consider additional antihypertensives:

(A) Nitroglycerin, nicardipine, nitroprusside, or fenoldopam titrated to effect are viable options (see Tables 9 and 10 for dosing and considerations).

(B) Verapamil and diltiazem decrease coronary vasospasm associated with acute cocaine intoxication (Am J Cardiol 1994;73:510-3).

(C) Controversy exists regarding the use of β-blockers.

- Labetalol has shown conflicting results regarding ability to control MAP but does not alleviate cocaine-induced coronary vasoconstriction.
- Consensus opinion recommends β-selective antagonists only if full α-antagonism is used first.

iv. Blood pressure variability (BPV)

(a) Concept of BPV emerging as a key therapeutic target in various populations (Stroke 2014;45:2275-9; Eur J Neurol 2013;20:1277-83; J Cardiothorac Vasc Anesth 2014;28:579-85).

(b) BPV is often expressed as the standard deviation of SBP, MAP, DBP, or the area under the curve of time spent outside of blood pressure target.

(c) In the intracerebral hemorrhage population, decreased BPV has been correlated with improved early neurological function (Eur J Neurol 2013;20:1277-83), favorable outcome (Stroke 2014;45:2275-9), and decreased death or major disability (Lancet Neurol 2014;13:364–73).

(d) Agent selection can influence BPV.

(1) Compared with labetalol, nicardipine has demonstrated superior results regarding BPV (Neurocrit Care 2013;19:41-47; Neurocrit Care 2008;9:167-176), but impact on clinical outcomes has not been demonstrated.

(2) In the cardiac surgery population, clevidipine demonstrated better perioperative BPV compared with nitroglycerin or sodium nitroprusside but not compared with nicardipine (Anesth Analg 2008;107:1110-1121) and was associated with decreased time to extubation and postoperative length-of-stay (J Cardiothorac Vasc Anesth 2014;28:579-85).

(e) Unclear what the future clinical impact will be on other populations, how agent selection will influence BPV, but should be an area of future research.

d. All intravenous medications should be transitioned to oral medications as soon as possible.

i. Oral antihypertensives should be initiated within 24 hours.

ii. Medication history and reconciliation can assist in resuming home regimens.

iii. Additional or new agents should be selected according to disease-specific indications.

Patient Case

7. B.B. is a 44-year-old man with no significant medical history who presents to the ED with a ripping sensation in his chest. His social history includes cigarette smoking, 1.5 packs/day for the past 20 years. Chest radiography in the ED reveals mediastinal widening. Cardiac enzymes are within normal limits. Laboratory values include sodium 135 mEq/L, potassium 4.3 mEq/L, HCO_3- 24 mEq/L, SCr 0.55 mg/dL, glucose 110 mg/dL, DBil 0.2 mg/dL, and AST 39 U/L. B.B. is rushed for a chest CT and angiography, which reveal an acute type A and B aortic dissection. His vital signs include BP 208/140 mm Hg and HR 120 beats/minute. Which is the most appropriate management for B.B.?

A. Use esmolol to achieve goal of 25% reduction in MAP during the first 60 minutes.

B. Use lisinopril and hydrochlorothiazide to achieve BP reduction goal to 160/100 mm Hg during the first 24 hours.

C. Use labetalol to achieve 25% reduction in MAP and HR less than 60 beats/minute in the first 60 minutes.

D. Use esmolol with or without nitroprusside to achieve SBP less than 100 mm Hg and HR less than 60 beats/minute as soon as possible.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

Because rescuer fatigue is common and may lead to inadequate compression quality, it is recommended to change rescuers every 2 minutes, with no more than 5 seconds between changes (Answer A is incorrect). Compressions are vital because they increase intrathoracic pressure and directly compress the heart, leading to oxygen delivery to the vital organs (Answer B is correct). Specific aspects of chest compression quality are necessary. These include a rate of 100–120 compressions per minute at a depth of 2–2.4 inches in adults, allowing for recoil after each compression; placement of the patient on a hard surface (e.g., backboard); and minimization of interruptions (Answer C is incorrect). Outcomes, including neurologically intact survival, ROSC, and possibly overall survival, are linked to minimizing interruptions in chest compressions. Because of this, it is recommended that interruptions (e.g., pulse checks and intubation) be less than 10 seconds and that chest compressions be resumed immediately (Answer D is incorrect).

2. **Answer: C**

Cardiac arrest patients have minimal blood flow, and oxygenation/ventilation requirements are lower; the new recommendation is to provide 1 breath every 5–6 seconds (10–12 breaths/minute) until an advanced airway is in place (Answer C is correct). Although the optimal ratio is unclear and chest compressions appear to be more vital to resuscitation, other ratios cannot currently be recommended (Answer A is incorrect). It is clear, however, that excessive ventilation can lead to decreased venous return and gastric inflation, which can lead to aspiration, regurgitation, and impacts on outcomes. In this case, a bag-mask ventilator is available, and more than one rescuers are involved, so the bag-mask ventilator should be used (Answer B is incorrect). In single health care provider rescuer situations, the bag-mask ventilator should never be used, and mouth-to-mouth or mouth-to-barrier resuscitation is recommended. In a single nonmedical rescuer situation, hands-only CPR is recommended. Advanced airways can be considered but should be placed only by experienced and trained personnel. Bag-mask ventilation can provide adequate oxygenation/ventilation until an airway can be secured (Answer D is incorrect).

3. **Answer: A**

Three vital actions with VF aid in survival: call emergency response team (already accomplished in case), begin CPR (must be initiated in case), and deliver shock (must occur in case) (Answer A is correct). Pacing can be effective in overriding stable VT but should not be used in the cardiac arrest or hemodynamically unstable patient (Answer B is incorrect). It is currently unclear whether postponing defibrillation for the provision of chest compressions first is of benefit, but it is clear that chest compressions should be initiated until the defibrillator is ready, charged, and set to deliver the shock because this increases the likelihood of success with defibrillation (Answer C is incorrect). Because time in VF predicts survival, and the longer patients are in VF the more difficult it is to terminate the arrhythmia, alternative treatments such as medications should not impede the provision of defibrillation (Answer D is incorrect).

4. **Answer: D**

After the advanced airway is in place, it is crucial to confirm placement in order to provide the intended oxygenation/ventilation. The confirmation should occur with both clinical and objective measurements (Answer D is correct). These include a physical assessment of the chest and epigastrium, end-tidal CO_2 monitoring, and/or continuous waveform capnography. In most cardiac arrests (particularly in this patient's pVT), airway management should not impede the provision of CPR and/or defibrillation (when defibrillation is indicated) (Answer B is incorrect). After the advanced airway is in place, 100% oxygen should be delivered to optimize the arterial oxygen saturation (Answer C is incorrect). In the cardiac arrest population, this has not been shown to carry the same toxicity as in other populations. Furthermore, after advanced airway is placed, compressions should be administered at a rate of 100–120 compressions per minute continuously, with breaths every 6 seconds (Answer A is incorrect).

5. **Answer: B**

In all cardiac arrests, the treatable causes (i.e., H's and T's) should be reviewed and addressed, if possible (Answer B is correct). In patients for whom the laboratory and diagnostic data are known, the information should be reviewed while CPR is being provided. In patients for whom the information is unknown, clinical evaluation and attainment of information should occur, when possible. This retrieval of information, together with the administration of medications and advanced airway placement, should never impede on the provision of CPR or defibrillation, if indicated, because defibrillation (for VF and pVT)) and CPR are the only strategies that have been shown to affect survival from cardiac arrest (Answer A is incorrect). Pulseless electrical activity is not a wide complex dysrhythmia, and defibrillation would not be indicated (Answer C is incorrect). Post-cardiac arrest care is crucial in the prevention of re-arrest and, in temperature control, can significantly affect neurologic outcomes (Answer D is incorrect).

6. **Answer: D**

In general, it is important to remember that medication administration benefits only myocardial blood flow, ROSC, and possibly survival to hospital admission in cardiac arrest. Medication administration should never impede the provision of CPR and/or defibrillation. Central administration, if already available, is preferred for several reasons. These include higher peak concentrations, shorter circulation time, more standard dosing, and the lack of additional administration techniques needed (Answer D is correct). Endotracheal administration is an option, but only NAVEL (naloxone, atropine, vasopressin, epinephrine, and lidocaine) medications can be administered, the optimal doses are unknown, and medications must be diluted before administered (Answer A is incorrect). Given that this patient is in VF arrest, amiodarone, for example, could not be administered by endotracheal administration if it were indicated. Peripheral administration can be used and is the most common route of administration given that most hospitalized patients have it already, but it requires an additional bolus of fluid afterward and has a longer circulating time than does central administration (Answer B is incorrect). Intraosseous can also be used, with the caveat that tibial intraosseous administration is similar to peripheral administration and requires training to master the technique for placement (Answer C is incorrect).

7. **Answer: B**

Temperature control improves neurologic recovery when initiated, optimally within 2 hours but in up to 6–8 hours after VF cardiac arrest (application to all forms), and used for 12–24 hours (Answer C is incorrect). The goal temperature is 32°C–36°C. Data suggest there is no benefit of 33°C versus 36°C in improvement of survival or neurologic outcomes (Answer D is incorrect). If temperature control will be used, close monitoring of complications should occur. These complications include hyperglycemia caused by decreased insulin production and peripheral activity (Answer A is incorrect), bradycardias, enzymatic slowing (including CYP system), increased incidence of sepsis and infections, coagulopathies, decreased glomerular filtration, and shivering (Answer B is correct).

8. **Answer: D**

This patient is experiencing a hypertensive emergency with his target organ damage being an acute aortic dissection. Aortic dissection is one of the individual hypertensive emergencies that has a specific mechanism of worsening (propagation) from BP and shear stress, which require both rapid BP and HR control. Given the gravity of propagation, goals for aortic dissection are HR less than 60 beats/minute and SBP less than 100 mm Hg within minutes, if possible (Answer A is incorrect). This can be accomplished with a single agent like labetalol, which will control HR with its β-antagonist properties and decrease BP (afterload) with its α-antagonist properties (Answers B and C are incorrect). Esmolol can also be used as first line but will likely require an additional afterload-reducing agent such as nitroprusside (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

The largest portion of adult cardiac arrests are caused by cardiovascular, not respiratory, events (Answer A is incorrect). In addition, this patient was on room air immediately before the event, which could suggest his respiratory status was stable and unlikely to lead to cardiac arrest. Advanced airways and medications have only been shown to facilitate ROSC in cardiac arrest in contrast to chest compressions and defibrillation (if indicated), which can improve survival. Because of this, CPR should begin immediately for this patient before line placement to facilitate medication delivery (Answer B is incorrect), starting with chest compressions in accordance with the BLS guidelines with pads placed simultaneously to facilitate rapid defibrillation if the patient's rhythm reveals a shockable rhythm (Answer C is correct; Answer D is incorrect).

2. **Answer: A**

The cornerstone of therapy for VF cardiac arrest is rapid defibrillation (Answer A is correct). The recommended dosage of voltage for biphasic defibrillators is 200 J or the manufacturer's recommendation (often the same dosage). Although amiodarone is in the treatment algorithm for VF cardiac arrest, it is reserved and recommended for refractory VF cardiac arrest, which is defined as defibrillation refractory (Answer B is incorrect). Therefore, defibrillation should occur first. Atropine has been removed from the cardiac arrest algorithms for PEA and asystole because of a lack of benefit on outcomes and should not be considered for VF cardiac arrest (Answer C is incorrect). Pacing has not shown benefit in cardiac arrest and should not be used (Answer D is incorrect).

3. **Answer: B**

Because the rhythm detected is PEA and no longer VF, the cornerstone of therapy changes from giving defibrillation (Answer A is incorrect) to giving high-quality chest compressions and addressing the treatable causes of cardiac arrest (H's and T's) (Answer B is correct). Lidocaine is reserved for refractory VF/pVT) (defined as defibrillator refractory) when amiodarone is unavailable (Answer C is incorrect). Atropine was previously recommended for PEA/asystole, but in the 2010 ACLS guidelines it was removed because of a lack of data supporting any beneficial outcomes (Answer D is incorrect).

4. **Answer: C**

Temperature control is a consideration, according to the international guidelines for all patients with ROSC who remain comatose after a cardiac arrest (Answer A is incorrect). Although most well-designed and executed studies primarily enrolled patients with VF cardiac arrest, application is recommended for all patients with a cardiac arrest independent of rhythm. Although worsening transaminitis and hepatic enzymatic function slowing is likely to occur during hypothermia, neither of these principles would be considered a contraindication for hypothermia (Answer B is incorrect). Furthermore, renal function with respect to glomerular filtration worsens, which requires vigilant monitoring of renal function and close attention to renal dose modifications and serum concentration monitoring of medications when applicable (Answer C is correct). An additional complication of therapeutic hypothermia is an induced coagulopathy, which leads patients to be at risk of bleeding. Thrombolytics may carry specific indications for cardiac arrest (e.g., pulmonary embolism or acute coronary syndromes), but they would not be recommended empirically (Answer D is incorrect).

5. **Answer: B**

Temperature control improves neurologic recovery in patients after a cardiac arrest (Answer B is correct). Most patients included in randomized clinical trials have VF as the causative rhythm (Answers A and D are incorrect). Because of its impact on neurologic recovery, guideline recommendations have applied this literature to cardiac arrests of all rhythms, and many institutions have adopted this same recommendation. Recent studies targeting mild hypothermia (36°C vs. 33°C) have shown no difference regarding outcomes between the two modalities, and because of this, some question the utility of hypothermia at all in an era of potentially more advanced cardiac arrest care (Answer C is incorrect).

6. **Answer: C**

By definition, this patient is having a hypertensive emergency because she has an abrupt, severe increase in BP with target organ damage—in this case, potentially shock liver and vision changes. (Answer A is incorrect). The patient's SCr is not elevated from baseline and is thus not presently showing target organ damage (Answer

B is incorrect). This patient's D-dimer is normal as well, but even if it were elevated, this is not a specific marker of target organ damage (Answer D is incorrect). The patient has significant elevations in her transaminases, indicating injury to the liver and thus qualifying her for hypertensive emergency (Answer C is correct).

7. **Answer: C**

The patient should be initiated on nitroprusside for BP management (Answer C is correct). Although she has transaminitis, nitroprusside can be used safely in the first 24 hours in these patients. Cyanide accumulation would be a concern with extended use, but for the first 24 hours, the patient will be at minimal risk, and the benefit of rapid BP control outweighs any potential risk. Phentolamine would be reserved for hypertensive crisis that presents from a catecholamine crisis (Answer A is incorrect). Oral metoprolol might be an appropriate option to transition to after the emergency is resolved, but because of the target organ damage, more rapid reduction is needed using an intravenous agent such as nitroprusside (Answer B is incorrect). Enalaprilat is an option, but 10 mg every 6 hours would not be an appropriate starting dose because it would put the patient at risk of overshooting and, given the long duration of activity, could lead to unwanted consequences (Answer D is incorrect).

8. **Answer: A**

The initial goal reduction for this patient's BP, given that she is experiencing a hypertensive emergency, is a 25% reduction in MAP within the first 60 minutes (Answer A is correct). More rapid BP reductions may result in a lack of cerebral perfusion; therefore, they are not recommended (Answer B is incorrect). The patient is not experiencing any of the specific hypertensive emergencies (e.g., aortic dissection) that would call for a more rapid BP reduction. In addition, she is not experiencing a hypertensive emergency that would require a slower BP reduction (e.g., stroke) (Answers C and D are incorrect).

HEPATIC FAILURE/GI/ENDOCRINE EMERGENCIES

STEPHANIE N. BASS, PHARM.D., FCCP, BCCCP, BCPS

CLEVELAND CLINIC
CLEVELAND, OHIO

MOLLIE G. LUMPKIN, PHARM.D., BCCCP, BCPS

CLEVELAND CLINIC
CLEVELAND, OHIO

HEPATIC FAILURE/GI/ENDOCRINE EMERGENCIES

Stephanie N. Bass, Pharm.D., FCCP, BCCCP, BCPS

Cleveland Clinic
Cleveland, Ohio

Mollie G. Lumpkin, Pharm.D., BCCCP, BCPS

Cleveland Clinic
Cleveland, Ohio

Learning Objectives

1. Develop a treatment strategy to help manage and reduce the complications associated with acute liver failure (ALF).
2. Construct a plan for pharmacologic, nutritional, and surgical management of acute pancreatitis based on the severity of an episode.
3. Identify risk factors and treatment options for gastrointestinal fistulas, postoperative ileus, and postoperative nausea and vomiting.
4. Design a treatment plan for patients who present with an acute upper gastrointestinal bleed.
5. Differentiate between the main endocrine emergencies in the intensive care and their appropriate treatment regimens.

Abbreviations in This Chapter

ALF	Acute liver failure
AP	Acute pancreatitis
BG	Blood glucose
CIRCI	Critical illness–related corticosteroid insufficiency
CPP	Cerebral perfusion pressure
CT	Computed tomography
DILI	Drug-induced liver injury
DKA	Diabetic ketoacidosis
ED	Emergency department
ERCP	Endoscopic retrograde cholangiopancreatography
GI	Gastrointestinal
HHS	Hyperosmolar hyperglycemic state
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalized ratio
MRI	Magnetic resonance imaging
NAI-ALF	Non–acetaminophen-induced acute liver failure
NG	Nasogastric
NJ	Nasojejunal
NSAID	Nonsteroidal anti-inflammatory drug
POI	Postoperative ileus
PONV	Postoperative nausea and vomiting
PPI	Proton pump inhibitor
SIRS	Systemic inflammatory response syndrome
T_3	Triiodothyronine
T_4	Thyroxine
TIPS	Transjugular intrahepatic portosystemic shunt
TPN	Total parenteral nutrition
TSH	Thyroid-stimulating hormone
UGIB	Upper gastrointestinal bleeding

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.

A 25-year-old woman is brought to the emergency department (ED) after a suspected overdose of acetaminophen. The time of ingestion is unknown. On presentation, her acetaminophen concentration is undetectable, but her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations are 3500 IU/L and 2500 IU/L, respectively. The patient is markedly confused with incoherent speech, but arousable. Other pertinent laboratory values include bilirubin 3.0 mg/dL and alkaline phosphatase 500 IU/L. White blood cell count is 12 × 10^3 cells/mm^3, platelet count is 90,000/mm^3, and international normalized ratio (INR) is 2.6.

1. Which option best represents the two signs or symptoms that would qualify this patient for a diagnosis of acetaminophen-induced acute liver failure (ALF)?
   A. Jaundice and encephalopathy.
   B. Thrombocytopenia and encephalopathy.
   C. Coagulopathy and encephalopathy.
   D. Leukocytosis and encephalopathy.

2. Which is the most appropriate treatment for her suspected acetaminophen-induced ALF?
   A. Give intravenous acetylcysteine 21-hour regimen, continuing if necessary until signs and symptoms of ALF have resolved.
   B. Acetylcysteine therapy is not indicated at this time because her acetaminophen concentration is undetectable.
   C. Give oral acetylcysteine 72-hour regimen.
   D. Oral acetylcysteine or intravenous acetylcysteine may be used because the two routes are similarly efficacious.

3. A 46-year-old man presents with alcohol-induced severe acute pancreatitis (AP). Pertinent medical history includes alcoholic cirrhosis and several admissions for aspiration pneumonia secondary to hepatic encephalopathy. He is given intravenous fluids for initial volume resuscitation with lactated Ringer solution. Which action would be best for the patient's nutrition?

   A. Give nothing by mouth (i.e., kept NPO) to rest the pancreas until AP is resolved.
   B. Initiate total parenteral nutrition (TPN).
   C. Give enteral feeding by the nasogastric (NG) route.
   D. Give enteral feeding by the nasojejunal (NJ) route.

4. A 37-year-old woman presents after a Roux-en-Y gastric bypass for morbid obesity. Her postoperative course was complicated by the formation of an enterocutaneous fistula, fevers, and leukocytosis. She was initiated on broad-spectrum antibiotics, and a wound vacuum-assisted closure was placed on her fistula site to help with drainage and healing. Her fistula output was 570 mL/day yesterday, and today, it was 250 mL/day. Which statement is most accurate regarding her fistula output between the two recordings?

   A. Her output would be defined as a low output on both days.
   B. Her output would be defined as a high output that has converted to a low output.
   C. Her output would be defined as a high output that has converted to a moderate output.
   D. Her output would be considered moderate on both days.

5. A 68-year-old man presents for a large bowel resection. Given the high incidence of postoperative ileus (POI) with this procedure, he is initiated on alvimopan before surgery. To reduce the cardiovascular risk associated with alvimopan, the U.S. Food and Drug Administration (FDA) placed a restriction on alvimopan use that has been implemented through the EASE (ENTEREG Access Support & Education) program. Which best represents that restriction?

   A. Start continuous electrocardiogram (ECG) monitoring on initiation to monitor for corrected QT (QTc) prolongation.
   B. Use is restricted to short term with a limit of 15 doses.
   C. Decrease alvimopan dose to 6 mg twice daily.
   D. Use is contraindicated in patients with previous myocardial infarction.

6. A 40-year-old woman presents for elective abdominal surgery to remove a malignancy from her liver. Given the extensiveness of the surgery, the expected use of volatile anesthetics, and the use of perioperative opioids, a multimodal plan is developed to avoid postoperative nausea and vomiting (PONV). Which best describes the timing of prophylactic administration with respect to surgery?

   A. Dexamethasone 4 mg intravenously given at the end of surgery.
   B. Ondansetron 4 mg intravenously given when inducing anesthesia.
   C. Neurokinin-1 receptor antagonist (aprepitant 40–125 mg) given at the end of surgery.
   D. Droperidol 0.625–1.25 mg intravenously given at the end of surgery.

7. A 69-year-old woman presents to the surgical intensive care unit (ICU) at your institution with upper gastrointestinal bleeding (UGIB) caused by a gastric ulcer. She has lost a significant amount of blood because of the bleed and currently requires blood transfusions. As part of her diagnostic workup to determine the etiology of her ulcer, she tests positive for a *Helicobacter pylori* infection. Which best reflects an inappropriate treatment option for her?

   A. Octreotide 50 mcg bolus, followed by 50 mcg/hour for 72 hours.
   B. Treatment with a proton pump inhibitor (PPI)/antibiotic combination for 14 days.
   C. A therapeutic endoscopy within 24 hours.
   D. Blood transfusions to maintain hemoglobin greater than 7 g/dL.

8. Which set of laboratory abnormalities best reflects those that patients in thyroid storm typically present with?

   A. High thyroid-stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4) concentrations.
   B. Low TSH, high T_3, and high T_4 concentrations.
   C. Low TSH, high T_3, and low T_4 concentrations.
   D. Low TSH, low T_3, and low T_4 concentrations.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
   a. Task A: 1, 2, 4
2. Domain 2: Therapeutic and Patient Management
   a. Task A: 1, 4, 6
   b. Task B: 4, 5, 6, 9, 10, 11, 13, 15
   c. Task C: 1

I. ACUTE LIVER FAILURE

A. Epidemiology
  1. Incidence of ALF is less than 10 cases per 1 million individuals per year (2000 cases per year in the United States), though morbidity and mortality are exceedingly high with ALF. Multiorgan failure and death occur in as many as 50% of patients.
  2. ALF accounts for less than 10% of liver transplants annually in the United States.
  3. ALF can occur in any age and demographic group, though the etiology of ALF is sometimes geographically dependent. Viral hepatitis cases are more common in developing countries, whereas toxin-related cases (e.g., those related to acetaminophen) occur more often in developed countries.
  4. The most common causes in the United States are drug induced, viral, autoimmune, and shock. Drug-induced causes, primarily acetaminophen, account for about 50% of the ALF cases in the United States. About 15% have no identifiable cause.
  5. The mortality rate has decreased significantly during the past few decades because of advances in medical care and early consideration for liver transplantation. Survival rates for ALF now exceed 65%, whereas before early transplantation, survival rates were less than 15%.

B. Definitions
  1. ALF is defined by the U.S. Acute Liver Failure Study Group (ALFSG) and the American Association for the Study of Liver Diseases (AASLD) as evidence of liver-induced coagulopathy, defined as an INR of 1.5 or greater, and any degree of mental alteration (encephalopathy) in a patient without preexisting liver failure and with an illness duration less than 26 weeks.
     a. ALF is in contrast to ACLF (acute-on-chronic liver failure), which is a syndrome defined on the basis of acute decompensation of chronic liver disease and presence of multiorgan failure.
  2. ALF may be further differentiated according to the time to encephalopathy after the onset of jaundice. These intervals typically provide clues regarding the cause of the ALF; however, the differentiation itself generally has no prognostic implications distinct from the causes themselves.
     a. Hyperacute ALF: Encephalopathy occurs less than 7 days after the onset of jaundice. This subclass of ALF is typically caused by acetaminophen toxicity or ischemic hepatitis and is associated with higher rates of transplant-free survival defined as survival free of liver-related death or liver transplantation. Patients tend to have high-degree encephalopathy at presentation and a higher incidence of cerebral edema, albeit a better prognosis overall.
     b. Acute ALF: Encephalopathy occurs 7–21 days after the onset of jaundice. Common causes of acute ALF include viral hepatitis. These patients have a high incidence of cerebral edema, but unlike in hyperacute ALF, lower rates of transplant-free survival.
     c. Subacute ALF: Encephalopathy occurs more than 21 days and less than 26 weeks after the onset of jaundice. Typical causes are drug induced or indeterminate. This subclass is associated with lower transplant-free survival, though patients have less marked coagulopathy and encephalopathy at presentation and may more often develop renal failure and portal hypertension.

C. Diagnosis and Disposition
  1. An unexplained elevated INR in a patient presenting with encephalopathy requires further evaluation for ALF because the combination of these two symptoms is very specific to ALF.
  2. In ALF, certain markers of chronic liver disease (e.g., jaundice, ascites, right upper quadrant pain, portal hypertension) may not be present.
  3. Additional physical examination, laboratory analysis, and imaging necessary for the diagnosis and workup of ALF are shown in Table 1.

4. Patients with any degree of encephalopathy should be transferred to an ICU, ideally with contact to a transplant center, because rapid progression can occur.

Table 1. Diagnostic Approach to a Patient with Suspected ALF

Diagnostic Work-up	Procedure
History	Assess timing of symptom onset
	Assess for exposure history to viruses, drugs (e.g., acetaminophen), or toxins (e.g., mushrooms)
	Assess substance abuse history
Physical examination	Normal signs of chronic liver disease (e.g., ascites, jaundice, right upper quadrant pain) may not be present
	Assess encephalopathy grade
Laboratory analysis	Basic metabolic panel, CBC, liver function tests, coagulation tests, arterial blood gas, acetaminophen concentrations, ammonia, toxicology screen, blood typing
	Viral serologies
	Liver biopsy useful for determining autoimmune hepatitis or ALF associated with HSV
Imaging	Hepatic imaging studies (computed tomography [CT], ultrasonography) may be used to detect a thrombus of the hepatic vein

ALF = acute liver failure; CBC = complete blood cell count; HSV = herpes simplex virus.

Adapted from: Lee WM. Acute liver failure. Semin Respir Crit Care Med 2012;33:36-45.

Table 2. Causes of ALF in the United States

Cause of ALF	Proportion of Cases
Acetaminophen	46%
Indeterminate	12%
Non-acetaminophen drug induced	11%
Hepatitis B	7%
Autoimmune	7%
Ischemic	7%
Hepatitis A	1.5%
Wilson disease	1.2%
Pregnancy	1%
Budd-Chiari	0.7%
Other	7%

ALF = acute liver failure.

Adapted from: Stravitz RT, Lee WM. Acute liver failure. Lancet 2019;394:869-81.

D. Causes (Table 2)
  1. Acetaminophen
    a. Acetaminophen overdose is responsible for almost 50% of ALF cases in the United States. Acetaminophen overdose is considered the primary cause of ALF in the United States and Europe, and it was responsible for 70,000 health care encounters and 300 deaths in the United States in 2005.

  b. Unlike most other types of drug-induced liver injury (DILI), acetaminophen-induced liver failure is dose-dependent and predictable, and it is typically associated with doses above 10 g/day (or more than 200 mg/kg/day) in 24 hours or more than 6 g/day (around 150 mg/kg/day) for 48 hours in adults.
  c. Rates of ALF caused by acetaminophen have increased during the previous 2 decades.
  d. If not treated in the early stages (i.e., before the development of encephalopathy), the mortality rate is around 20%–40%.
  e. Acetaminophen-induced ALF typically presents as hyperacute liver failure and is defined by four stages of progression:
    i. Preclinical: Occurs within the first 24 hours of ingestion. Typically associated with minimal or no signs or symptoms of hepatotoxicity
    ii. Injury: Occurs 24–72 hours after ingestion. Associated with marked elevation in liver transaminases
    iii. Failure: Occurs 72–96 hours after ingestion. Associated with peak liver injury including encephalopathy, coagulopathies, and jaundice
    iv. Recovery: Occurs 1 week after ingestion if patient survives through failure stage. Recovery may be prolonged in critically ill patients who present with fulminant liver failure.
  f. Additional information on background, pathophysiology, and treatment of acetaminophen overdose can be found in the Toxicology review chapter.
2. Non–acetaminophen-induced acute liver failure (NAI-ALF)
  a. DILI
    i. The incidence of DILI caused by drugs other than acetaminophen is rare, at a rate of approximately 11% of ALF cases per year.
    ii. Unlike acetaminophen-induced liver failure, DILI is rarely the result of dose-related toxicity, and most cases are idiosyncratic.
    iii. DILI typically presents as a subacute ALF, with most cases occurring within the first 6 months after drug initiation. However, some drugs (e.g., nitrofurantoin, minocycline, statins) have the potential to cause DILI 6 months or more after initiation.
    iv. Transplant-free survival is low for these patients (about 30%), and most patients will require transplantation.
    v. DILI is ultimately a diagnosis of exclusion. The American College of Gastroenterology (ACG) guidelines for the management of DILI recommend a specific workup for viral hepatitis, autoimmune hepatitis, Wilson disease, and Budd-Chiari syndrome before diagnosis of DILI.
    vi. To identify potential culprit medications, a detailed patient medication history should be obtained, including herbal medications. Classes of drugs commonly associated with DILI include antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants, which together account for almost two-thirds of those attributable to DILI.
    vii. Scoring systems such as the RUCAM (Roussel Uclaf Causality Assessment Method) have been developed to assess the causality attribution for suspected DILI. These scoring systems give points on the basis of timing of exposure and liver function tests, risk factors for DILI, competing medications and diagnoses, and rechallenge information. Higher scores indicate a higher likelihood of drug cause.

- viii. The pattern of liver injury may also help identify drug causes. Hepatocellular injury (characterized by a marked elevation in transaminases with marginal increase in bilirubin and alkaline phosphatase) is associated with certain drug causes, whereas cholestatic injury (characterized by a marked elevation in bilirubin and alkaline phosphatase with only minimal increases in transaminases) is associated with other drug causes of DILI. Other drug causes of DILI exhibit a mixed pattern of liver injury in which both hepatocelluar injury and cholestatic injury will be present. See Appendix 1 for a list of medications linked to DILI and associated pattern of liver injury.

b. Viral
  - i. Infection with hepatitis A, B, or E is the primary etiology of ALF in the developing world and has become a relatively infrequent cause of ALF in the United States (about 12%).
  - ii. Hepatitis A
    - (a) Accounts for about 2% of ALF cases in the United States
    - (b) Transmission is usually by the fecal-oral route.
  - iii. Hepatitis B
    - (a) Rates of hepatitis B–induced ALF have fallen significantly in the past few decades; however, hepatitis B is still the cause of about 7% of ALF cases per year.
    - (b) ALF secondary to hepatitis B is often caused by reactivation of chronic or inactive hepatitis B during times of immunosuppression (e.g., chemotherapy and high dose steroids). To prevent reactivation, patients who are positive for HBsAg (hepatitis B surface antigen) and who are to begin immunosuppressive regimens require antiviral prophylaxis with a nucleos(t)ide analog, typically entecavir, lamivudine, or tenofovir. Treatment, which is usually initiated before immunosuppression, continues during immunosuppressive therapy and for 6 months thereafter.
  - iv. Hepatitis E
    - (a) Rare cause of ALF in the United States; however, hepatitis E–induced ALF is a significant cause of ALF in countries where it is endemic, such as Russia, Pakistan, Mexico, and India.
    - (b) Hepatitis E–induced ALF tends to be more severe in pregnant women, and hepatitis E can be transmitted to neonates during acute infections in pregnant women.
  - v. Herpes simplex virus (HSV)
    - (a) HSV is rarely a cause of ALF; however, cases have been reported, particularly in immunocompromised and pregnant patients (usually in the third trimester).
  - vi. Viral hepatitis–induced ALF generally presents as acute or subacute liver failure with an onset of symptoms greater than 1 week after onset of jaundice.
  - vii. Globally, mortality rates are greater than 50% because of ALF from hepatitis A and E in the developing world; however, mass vaccination and better public health standards have helped reduce the incidence of viral infections in the developed world.

c. Acute ischemic injury
  - i. Often called “shock liver,” acute ischemic injury may lead to ALF after cardiac arrest, any period of significant hypovolemia or hypotension, or during severe congestive heart failure.
  - ii. Documented hypotension is not always evident with acute ischemic injury. Drug-induced hypotension or hypoperfusion may also cause acute ischemic injury, such as with cocaine and methamphetamine.
  - iii. Typical laboratory presentation includes markedly elevated aminotransferase concentrations. In addition, simultaneous renal dysfunction and other markers of hypoperfusion may be present.
  - iv. Acute ischemic injury is classified as a hyperacute ALF, which generally resolves with resolution of the circulatory problem.

- d. Mushroom poisoning
  - i. Typically caused by the *Amanita phalloides* spp. of mushrooms
  - ii. Mushroom poisoning is classified as a hyperacute ALF with an onset of symptoms within 24 hours after ingestion. In addition to hepatotoxicity, patients with mushroom poisoning present with severe gastrointestinal (GI) symptoms including nausea, vomiting, diarrhea, and abdominal cramping.
- e. Wilson disease
  - i. Rare cause of ALF; implicated in approximately 1% of cases per year, mostly affecting young people
  - ii. Wilson disease is a rare disorder that causes accumulation of copper in the body. Diagnosis is characterized by an abrupt onset of Coombs-negative hemolytic anemia with serum bilirubin greater than 20 mg/dL. Other diagnostic laboratory findings include low serum ceruloplasmin, presence of Kayser-Fleischer rings, and high urinary and hepatic copper concentrations.
  - iii. Patients who present with fulminant liver failure secondary to Wilson disease have exceedingly high mortality rates without transplantation.
- f. Autoimmune hepatitis
  - i. Autoimmune hepatitis is considered a chronic inflammatory disease; however, patients can still be considered to have ALF if they had rapid deterioration of symptoms.
  - ii. About 20% of patients with stable disease will have ALF, which is typically instigated by an environmental trigger.
- g. Budd-Chiari syndrome
  - i. Budd-Chiari syndrome is caused by an acute hepatic vein thrombosis. Presenting symptoms include abdominal pain, ascites, and frank hepatomegaly. Patients who initially present with ALF require anticoagulation with heparin as initial therapy; in those who do not respond anticoagulation, transjugular intrahepatic portosystemic shunt (TIPS) may be considered.
  - ii. In patients with ALF who do not respond to medical or therapeutic interventions, transplantation may be required.
- h. Acute fatty liver of pregnancy/hemolysis, elevated liver enzymes, low platelets (HELLP)
  - i. Toward the end of pregnancy, a small percentage of women will develop rapidly progressive hepatic failure that is generally associated with three hallmark signs: jaundice, coagulopathy, and low platelets, also known as HELLP. Features of pre-eclampsia such as hypertension and proteinuria are common with HELLP.
  - ii. HELLP is associated with increased mortality for both the fetus and the mother.
  - iii. Requires emergency delivery of fetus, after which symptoms should resolve. If ALF fails to improve after delivery of the fetus, liver transplant evaluation is necessary.

E. Complications

- 1. ALF affects almost every organ system in the body:
  - a. Neurologic
    - i. Cerebral edema and elevated intracranial pressures (ICPs) are the most serious complications of ALF. Uncontrolled edema and elevated ICPs can lead to uncal herniation and are usually fatal. Cerebral edema may also lead to tissue hypoxia, which may result in long-term neurologic deficits.
      - (a) Elevated ICPs can be caused by several factors, but osmotic shifts in the brain, inflammation, and neurotoxins are thought to be the primary causes.

(b) Because ammonia is converted to osmotically active glutamine, concentrations have been correlated with both encephalopathy and cerebral edema. Ammonia concentrations greater than 200 mcg/dL are associated with cerebral herniation, whereas concentrations less than 75 mcg/dL are rarely associated with hepatic encephalopathy. In ALF, either because of impaired hepatocyte activity or the abnormal shunting of venous flow away from the liver, normal mechanisms to detoxify and clear ammonia are no longer effective.

ii. Encephalopathy is considered an indicator for the clinical presentation of cerebral edema. Encephalopathy can be difficult to identify and may present initially as agitation and confusion; however, it may progress rapidly to unresponsiveness. Table 3 gives useful guidelines for measuring the severity of encephalopathy.

iii. Occurrence of cerebral edema and elevated ICPs is generally related to the severity of hepatic encephalopathy. Patients with grade I and grade II encephalopathy rarely have cerebral edema, whereas cerebral edema is present in about 25%–35% of patients with grade III encephalopathy and about 65%–75% of patients with grade IV encephalopathy.

Table 3. Grades of Encephalopathy

Grade of Encephalopathy	Signs and Symptoms
Grade I	Changes in behavior with minimal change in level of consciousness
Grade II	Gross disorientation Drowsiness Possibly asterixis Inappropriate behavior
Grade III	Marked confusion Incoherent speech Sleeping most of the time but arousable to vocal stimuli
Grade IV	Comatose Unresponsive to pain, decorticate or decerebrate posturing

Adapted from: Conn HO, Leevy CM, Vlehcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind randomized trial. Gastroenterology 1977;72:573-83.

b. Cardiovascular

i. The primary hemodynamic concern in ALF is low systemic vascular resistance, similar to cirrhosis. Additional hemodynamic effects in ALF include hyperdynamic circulation with high cardiac output and decreased effective circulating volume.

ii. Most patients are severely volume depleted on admission because of poor nutritional status and third spacing into the extravascular space and will initially require aggressive fluid resuscitation.

iii. In patients with an elevated ICP, maintaining adequate perfusion is essential to preserve adequate oxygen delivery to the brain. A common goal is to maintain a cerebral perfusion pressure (CPP) of at least 60 mm Hg. Higher mean arterial pressure (MAP) targets may be needed in these patients in order to maintain CPP goals. CPP = MAP − ICP.

c. Coagulopathy

i. ALF is defined by the presence of an elevated INR caused by decreased production, together with increased consumption, of coagulation factors.

ii. Consumption of platelets is also seen, and thrombocytopenia (150,000/mm^3 or less) is common.

iii. Despite these changes in coagulation parameters, thromboelastography studies of patients with ALF have shown that overall hemostasis in patients with ALF is maintained by compensatory mechanisms, even in patients with elevated INR values, potentially because of a reduction in hepatic synthesis of natural anticoagulants.

            iv. Spontaneous bleeding in patients with ALF, though uncommon, is capillary-type bleeding and usually results from mucosal bleeding in the stomach, lungs, or genitourinary system. Unlike chronic liver failure, bleeding from esophageal varices generally does not occur.
            v. Clinically significant bleeding that requires blood transfusions is rare in ALF.
        d. Renal
            i. Acute kidney injury with ALF is generally classified as either prerenal injury or acute tubular necrosis.
                (a) Prerenal azotemia typically is caused by vasodilatation owing to portal hypertension and is worsened by systemic hypoperfusion, similar to hepatorenal syndrome in patients with cirrhosis.
                (b) Acute tubular necrosis typically occurs secondary to drugs or toxins, such as acetaminophen or *Amanita* poisoning.
        e. Infection
            i. Patients with ALF are at high risk of infection because of prolonged ICU stays, the presence of indwelling foleys and central venous catheters in addition to intrinsic monocyte and neutrophil dysfunction. Infections are of particular concern because they may delay transplantation or be problematic during the postoperative period.
            ii. The most common infections in ALF are pneumonia, followed by urinary tract infections and bloodstream infections. The most commonly isolated organisms are gram-positive cocci (e.g., *Staphylococcus, Streptococcus*) and enteric gram-negative bacilli. Fungal infections, particularly those caused by *Candida*, occur in about one-third of patients with ALF.
        f. Metabolic abnormalities
            i. Lack of effective glycogenolysis and gluconeogenesis, caused by impaired hepatocyte function, places patients at high risk of hypoglycemia.
            ii. Symptoms of hypoglycemia can often be difficult to identify in patients with severe encephalopathy, whereas profound hypoglycemia can worsen an already altered mental state.
            iii. Hyponatremia is also common in patients with ALF, secondary to alterations in antidiuretic hormone from tissue hypoperfusion and renal dysfunction. Avoidance of hyponatremia is particularly important in patients with high-grade encephalopathy.
    2. Therapy must be multimodal to support each of the organ systems affected by ALF.

F. Management of ALF
    1. Antidotes
        a. Acetaminophen-induced ALF (see Table 4)
            i. Although most effective if given within the first hour, GI decontamination with activated charcoal may be of benefit for up to 4 hours after ingestion and does not reduce the effect of acetylcysteine.
            ii. Administration of acetylcysteine is recommended in all ALF cases in which acetaminophen is suspected as a cause.
                (a) Acetylcysteine can be given either orally or intravenously. Studies have shown similar outcomes between the two routes; however, in those studies, the main efficacy outcome of interest was development of hepatotoxicity. In patients already presenting with hepatotoxicity (as in ALF), intravenous acetylcysteine is recommended. The U.S. Acute Liver Failure Study Group recommends intravenous therapy for any of the following:
                    (1) Greater than grade I encephalopathy
                    (2) Hypotension
                    (3) If oral therapy cannot be tolerated (e.g., vomiting, compromised airway, ileus)

(b) Many poison centers may extend therapy beyond the recommended course if there is a detectable acetaminophen concentration or if ALT concentrations continue to remain elevated at the end of therapy, especially if therapy was initiated more than 8 hours after ingestion and baseline acetaminophen concentrations were greater than 300 mcg/mL when extrapolated on the Rumack–Matthew nomogram.

(c) Recent studies have evaluated alternative dosing strategies for patients with massive overdoses, including doubling the last bag (i.e., providing 200 mg/kg over 16 hours). Massive overdoses are considered ingestions with initial acetaminophen concentrations greater than 300 mcg/mL when extrapolated on the Rumack–Matthew nomogram, or a single ingestion greater than 30 g; doubling the last bag has been associated with reduced hepatotoxicity. However, these strategies must be further evaluated.

(d) Therapy may continue until the signs and symptoms of encephalopathy or coagulopathy resolve or until the patient receives a liver transplant. The 2023 ACG ALF guidelines note that duration of NAC treatment for APAP-induced ALF should be "individualized based on patient's clinical condition and laboratory values." (Am J Gastroenterol 2023:118:1128-53)

(e) Additional information on treatment of acetaminophen-induced ALF can be found in the Toxicology chapter.

Table 4. Acetylcysteine for Acetaminophen-Induced ALF

Route	Dose
Oral	Loading dose: 140 mg/kg × 1 dose Maintenance dose: 70 mg/kg every 4 hr × 17 doses (72 hr total)
IV	150 mg/kg (max 15 g) over 60 min, followed by 50 mg/kg (max 5 g) over 4 hr, followed by 100 mg/kg (max 10 g) over 16 hr (21 hr total)

IV = intravenous.

b. NAI-ALF

   i. Acetylcysteine may improve oxidative stress in NAI-ALF by acting as a free radical scavenger. In addition, acetylcysteine may improve both hepatic and systemic perfusion through its vasodilatory effects.

   ii. A multicenter randomized trial compared intravenous acetylcysteine with placebo for 72 hours (see Table 5) for treatment of NAI-ALF. Randomized patients were stratified according to coma grade, with most patients having a low-grade encephalopathy. There was no difference in the primary outcome of overall survival at 3 weeks between acetylcysteine and placebo; however, the transplant-free survival rate significantly increased with the use of acetylcysteine (40% vs. 27%, p=0.04).

      (a) The increase in transplant-free survival with acetylcysteine was mainly confined to the subgroup of patients with encephalopathy grade I and grade II (52% vs. 30% with placebo, p=0.01).

      (b) When outcomes were compared on the basis of each etiology of NAI-ALF, patients with DILI and hepatitis B virus had more improvement in overall survival and transplant-free survival from acetylcysteine compared with placebo than with other causes.

   iii. Intravenous acetylcysteine has also been studied for the treatment of NAI-ALF as a loading dose followed by a continuous infusion of 150 mg/kg over 24 hours until resolution of coagulopathy (INR less than 1.3). This strategy increased transplant-free survival compared with a historical cohort (96.4% vs. 23.3%, p<0.01); however, the strategy needs to be further evaluated.

iv. Oral acetylcysteine has also been evaluated for the treatment of NAI-ALF in a prospective non-interventional study in which it, compared with a historical cohort, was associated with reduced mortality. In this study, oral acetylcysteine was given as a 140-mg/kg loading dose, followed by 70 mg/kg every 4 hours for an additional 17 doses. However, at this time, only intravenous acetylcysteine has been studied in a randomized controlled trial for NAI-ALF.

Table 5. Acetylcysteine for NAI-ALF

Route	Dose
Intravenous	150 mg/kg over 1 hr, followed by 12.5 mg/kg/hr for 4 hr, followed by 6.25 mg/kg/hr for 67 hr

Patient Case

1. A 60-year-old woman with rheumatoid arthritis was initiated on azathioprine 3 months ago and now presents with NAI-ALF secondary to DILI. On presentation, her ALT and AST concentrations are 500 IU/L and 350 IU/L, respectively. Her INR is 1.7, and she is mildly confused and drowsy. Which intervention has been shown most effective for the treatment of NAI-ALF?
   A. Intravenous acetylcysteine 21-hour regimen.
   B. Intravenous acetylcysteine 72-hour regimen.
   C. Oral acetylcysteine 72-hour regimen.
   D. Oral glutamine supplementation.

c. Viral hepatitis
    i. Hepatitis B
        (a) Similar to prophylaxis, acute hepatitis B infection treatment requires a nucleos(t)ide analog: entecavir 1 mg daily or lamivudine 100 mg daily.
    ii. Herpes simplex virus
        (a) Patients with HSV ALF can be treated with high dose acyclovir 5–10 mg/kg intravenously every 8 hours for at least 7 days.
d. Mushroom poisoning
    i. Gastric lavage and activated charcoal may be beneficial for patients still having GI symptoms indicative of a recent ingestion.
    ii. Although data regarding efficacy are lacking, penicillin G or silibinin (silymarin or milk thistle) can be used as an antidote to α-amanitin, a toxin released after mushroom ingestion. Intravenous silibinin is guideline-preferred therapy based on the 2023 ACG guidelines, although this is a low-level recommendation; however, it is only available in United States through compassionate use, investigational drug access. Therefore, penicillin G is often used instead. Penicillin G directly competes with and inhibits the ability of the toxin to bind to plasma protein and penetrate the liver. Recommended dose of penicillin G for mushroom poisoning is 300,000 to 1 million units/kg/day given intravenously.
e. Autoimmune hepatitis
    i. High-dose intravenous corticosteroids (greater than or equal to 1 mg/kg prednisone equivalent or greater than or equal to 60 mg prednisone equivalent per day) should be initiated for patients who present with ALF secondary to autoimmune hepatitis. However, patients with progressive disease will require liver transplantation.

2. Management of neurologic complications
   a. Encephalopathy
      i. All medications that can cause sedation or confusion should be avoided (i.e., benzodiazepines, anticholinergics, etc.).
      ii. Grade I encephalopathy can typically be managed with close monitoring and without medication; grade II–IV encephalopathy should be treated in an ICU setting, if possible.
      iii. Given its ability to decrease serum ammonia concentrations and experience with treatment of hepatic encephalopathy in patients with cirrhosis, lactulose may be considered for patients with ALF with low-grade encephalopathy (e.g., grade I–II). The recommended dose is 20–30 g three or four times daily to produce 2 or 3 soft stools a day.
         (a) Despite its proposed benefits, retrospective data analyses of patients with ALF who receive lactulose therapy have not shown a benefit on encephalopathy or overall outcome.
         (b) In addition, lactulose has the potential to cause abdominal distension, which could be a concern for liver transplantation. Moreover, overuse of lactulose has the potential to cause intravascular depletion, which may further contribute to hemodynamic instability. Therefore, its effects may be harmful in the acute setting, particularly for patients with high-grade encephalopathy. In the 2023 ACG guidlines, the authors determine there is inconclusive evidence to recommend for or against the use of lactulose in the treatment of ALF.
         (c) A similar recommendation is made for the role of rifaximin for the treatment of encephalopathy in the 2023 ACG guidelines; namely, that there is inconclusive evidence for or against its use in this setting.
      iv. Some centers use high-flow continuous renal replacement therapy (CRRT) to remove ammonia in patients with high-grade encephalopathy. CRRT has been associated with lower ammonia levels within the first 3 days of ALF (median reduction in ammonia is 38% with CRRT compared with 23% for intermittent RRT and 19% for no RRT). In the 2023 ACG guidelines, early CRRT was recommended for patients with grade II encephalopathy or higher.
      v. Patients with grade III and grade IV encephalopathy should be intubated for airway protection and treated with minimal sedation to allow for more frequent neurologic assessments. If sedation is necessary, propofol is typically used because it can reduce cerebral blood flow and lower ICP.
   b. Seizures
      i. Seizures have the potential to increase ICP. Therefore, seizures should be controlled quickly with short-acting benzodiazepines. If seizures persist, antiepileptic agents should be scheduled.
      ii. Use of prophylactic antiepileptics is not recommended. Studies have shown that use of prophylactic phenytoin in patients with ALF has no impact on prevention of seizures, cerebral edema, or overall survival.
   c. Elevated ICPs
      i. ICP should be kept less than 20–25 mm Hg while preserving CPP of at least 60 mm Hg.
      ii. Routine ICP monitoring has not been shown to reduce mortality in patients with ALF, and routine placement of ICP monitors is not recommended. Clinicians may choose to place an ICP monitor in patients with high-grade encephalopathy (grades III and IV) to provide close monitoring of cerebral edema. In addition, some centers may use noninvasive ICP monitoring strategies such as transcranial Doppler ultrasound to avoid the risks associated with more invasive ICP monitor placement in these coagulopathic patients. However, these monitoring strategies should be reserved for centers with large neurocritical care and neurosurgical experience.

iii. Osmotic agents are used first line for control of ICP.
    (a) Mannitol has been used effectively in acutely reducing ICP in patients with ALF, though the effect is usually transient.
        (1) Mannitol is given as 0.5–1 g/kg intravenously once, which may be repeated to effect as long as the serum osmolality is less than 320 mOsm/L; however, mannitol is typically ineffective if the baseline ICP is greater than 60 mm Hg.
            (A) Serum osmolality is estimated based on serum sodium, glucose, and blood urea nitrogen based on the following formula: (Na x 2) + (glucose/18) + (blood urea nitrogen/2.8).
        (2) Adverse effects to consider for mannitol administration include fluid overload, particularly in patients with renal impairment, hyperosmolarity, hypotension, and hypernatremia.
        (3) Hypertonic saline bolus (23.4% 30-mL bolus or 3% 200- to 300-mL bolus) is an alternative to mannitol for acute reductions in ICP. Adverse effects include hypernatremia and hyperchloremia.
    (b) In patients with grade III or grade IV encephalopathy, multiorgan failure, or hemodynamic instability, prophylactic hypertonic saline (to goal 145–155 mEq/L) may be used to reduce the risk of cerebral edema.
        (1) In a small, randomized controlled trial, 30 patients with ALF and grade III or grade IV encephalopathy were randomized to receive prophylactic hypertonic saline to maintain a serum sodium of 145–155 mEq/L compared with patients maintained at near-normal serum sodium levels (137–142 mEq/L). The primary outcome, incidence of ICP defined as elevations greater than 25 mm Hg, was significantly decreased in the hypertonic saline group (20% hypertonic saline vs. 46.7% control, p=0.04).
        (2) Hypertonic saline in this study was administered as a 30% sodium chloride infusion by a syringe at 5–20 mL/hour; however, many preparation and dosing strategies have been used (e.g., 23.4% 30-mL bolus, 7.5% 2-mL/kg bolus, 3% 200- to 300-mL bolus, or continuous infusion), and the goal should be to target a serum sodium of 145–155 mEq/L.

iv. When severe ICP elevations do not respond to other measures, barbiturates such as pentobarbital may be used to control ICP.
    (a) Profound hypotension may limit barbiturate use in ALF when patients have hemodynamic instability at baseline. Patients may require vasopressors to maintain adequate MAP (and CPP) while receiving barbiturates.
    (b) Barbiturate clearance is significantly decreased in patients with ALF, which may limit clinicians' ability to perform neurological assessments for extended periods.

v. Hyperventilation to a $Pa\text{CO}_2$ of 25–30 mm Hg can restore cerebral autoregulation, which results in vasoconstriction and decreased ICP.
    (a) The effects of hyperventilation on ICP appear to be short-lived. A randomized controlled trial of prophylactic hyperventilation showed no benefit on cerebral edema and survival. In addition, there is concern that cerebral vasoconstriction with hyperventilation may worsen cerebral hypoxia.
    (b) Thus, hyperventilation currently plays no role in prevention of ICP and should only be considered for refractory treatment of acute ICP.

vi. Hypothermia (33°C–34°C) may control ICP in patients with ALF by lowering the production of ammonia and by decreasing the cerebral uptake of ammonia and cerebral blood flow. However, hypothermia for patients with ALF has not been compared with normothermia in controlled trials, and a recent retrospective cohort study showed no difference in overall and transplant-free survival when compared with normothermia. In addition, there are concerns about coagulation disturbances and increased risk of infection with hypothermia.

Patient Case

2. A 33-year-old man presents with ALF secondary to acetaminophen overdose. He is now 72 hours post-ingestion and is profoundly encephalopathic and unresponsive to pain on examination. An ICP monitor is placed, which shows acute elevations of 30 mm Hg. Which is most appropriate for the acute management of ICP elevations?
   A. Hypertonic saline continuous infusion to maintain serum sodium 145–155 mEq/L.
   B. Mannitol 0.5 mg/kg intravenously × 1.
   C. Hyperventilation to Pa_{CO_2} of 25–30 mm Hg.
   D. Thiopental continuous infusion.

3. Management of hemodynamic instability
   a. Patients should initially be resuscitated with 0.9% sodium chloride. Hypo-osmolar fluids including lactated Ringer solution (273 mOsm/L) should be avoided, if possible, in patients with grade III and grade IV encephalopathy because of the risk of cerebral edema. In addition, Plasma-Lyte (294 mOsm/L) could be used as an alternative to 0.9% sodium chloride (308 mOsm/L), given that it is not hypo-osmotic and would provide a balanced solution to avoid the risk of hyperchloremic metabolic acidosis.
   b. Vasopressors should be used if fluid resuscitation fails to maintain a MAP greater than 75 mm Hg or a CPP of at least 60 mm Hg.
      i. Norepinephrine is the vasopressor of choice in patients requiring vasopressor support.
      ii. Use of vasopressin is controversial for patients with ALF who have high-grade encephalopathy. One study of six patients with grade IV encephalopathy showed an increased ICP after 1 hour of terlipressin (a synthetic vasopressin analogue), though systemic hemodynamics were not significantly altered; however, a subsequent study did not show similar effects on ICP with terlipressin. Because there have been no similar studies of vasopressin in patients with ALF, its use in patients with ALF and high-grade encephalopathy should be cautioned. However, in the 2020 Society of Critical Care Medicine (SCCM) supportive care management guidelines for patients with acute liver failure as well as the 2023 ACG ALF guidelines, vasopressin is recommended to be added to norepinephrine with persistent shock, despite these concerns, although both guidelines note a low level of evidence.
4. Management of coagulopathies
   a. Although the INR may be elevated in patients with ALF, overall hemostasis is maintained through compensatory mechanisms.
   b. Because traditional measures of coagulation may be unreliable, guidelines suggest use of viscoelastic testing such as thromboelastography over measuring INR, platelets, and fibrinogen when available. In a small randomized trial of 60 cirrhotic patients, blood product transfusion was significantly reduced when guided by thromboelastography compared with traditional measures with no differences in bleeding complications. Unfortunately, these tests are not available at many institutions and traditional measures are often still required.
   c. In patients without acute bleeding or high-risk procedure such as ICP monitor placement, the routine correction of coagulopathy is not supported. For instance, in patients with an elevated INR without signs and symptoms of an acute bleed, INR should not be corrected using fresh frozen plasma. Vitamin K (5–10 mg) may be administered because many patients with ALF are deficient in vitamin K, further contributing to the coagulopathy of ALF. Intravenous administration is usually recommended because subcutaneous administration of vitamin K can lead to erratic absorption, and enteral absorption may also be unreliable.

- d. If clinically significant bleeding occurs, INR correction with fresh frozen plasma is warranted.
  - i. Guidelines recommend an INR correction to about 1.5 for clinically significant bleeding.
  - ii. If a fresh frozen plasma infusion alone does not adequately lower INR, recombinant activated factor VII (rFVIIa) may be administered. In a small nonrandomized study of 15 patients with fulminant hepatic failure, administration of rFVIIa at a dose of 40 mcg/kg temporarily improved coagulation parameters (i.e., INR less than 1.6) compared with patients receiving only fresh frozen plasma (100% vs. 0%, $p<0.002$). Although the improvements in coagulation were only temporary, patients in the rFVIIa group were able to have invasive procedures performed (e.g., ICP monitors placed) more often than were patients in the control group (100% vs. 38%, $p=0.03$).
  - iii. Data are limited on use of prothrombin complex concentrate (PCC) for reversing coagulopathy in ALF; however, it appears to be similar in efficacy to rFVIIa. A retrospective study in patients with cirrhosis found similar rates of INR reversal (1.5 or less) in patients who received either PCC (80%; $p=0.03$) and rFVIIa (87%; $p=0.04$), compared with FFP (27%). Therefore, PCC may be an option in cases for which the goal is to limit volume associated with FFP; however, INR-based dosing limits this use, and further study is warranted.
- e. To reduce the risk of spontaneous intracranial hemorrhage, platelet transfusions should be provided if the count drops to less than 15,000–20,000/mm^3 in the absence of bleeding.
  - i. If clinically significant bleeding occurs, patients should be transfused to a target platelet count greater than 50,000/mm^3.
  - ii. For invasive procedures, platelet counts should be 50,000–70,000/mm^3 to prevent bleeding, though thromboelastography data analyses suggest that a target of 100,000/mm^3 is ideal.
- f. Patients with ALF should be evaluated for venous thromboembolism prophylaxis based on traditional risk assessments (e.g., thrombocytopenia, recent and/or active bleeding, etc). Venous thromboembolism prophylaxis should not be withheld due to elevated INR because INR often overestimates hypercoaguability in patients with ALF. Selection of agent for prophylaxis is unclear. No studies have compared low-molecular-weight heparin with unfractionated heparin in patients with ALF; however, most studies of patients with cirrhosis support the use of LMWH, though the control group is no-prophylaxis.
- g. Histamine-2 receptor antagonists or PPIs should be initiated in patients with ALF to reduce the incidence of spontaneous GI bleeding.

5. Management of infectious complications
   - a. Antimicrobial prophylaxis is often given because infection remains the primary cause of death in patients with ALF. However, data analyses are limited on the benefit of antimicrobial prophylaxis in ALF. A retrospective cohort study of 1551 patients with ALF showed that prophylactic antibiotic therapy did not reduce the incidence of bloodstream infections (12.8% in the prophylaxis group vs. 15.7% in the non-prophylaxis group, $p=0.12$) and did not reduce 21-day mortality.
   - b. The 2023 ACG guidelines recommend against the routine use of prophylactic antimicrobials. Patients should be monitored closely for infection through surveillance cultures, and antimicrobials should be initiated promptly if the patient has any signs or symptoms of a systemic infection. Empiric administration is recommended for any of the following scenarios:
     - i. Positive surveillance cultures
     - ii. Progression to higher-grade encephalopathy
     - iii. Refractory hypotension
     - iv. Development of systemic inflammatory response syndrome (SIRS) criteria

G. Advanced Therapies for ALF
  1. Liver assist devices: The molecular adsorbent recirculating system (MARS) has been studied for the treatment of ALF. In a large propensity-matched study of 104 patients who received MARS for ALF (matched 4:1 to 416 controls), MARS significantly increased the odds of 21-day transplant-free survival (OR 1.9; 95% CI, 1.07–3.39; p=0.03).
  2. Transplantation
    a. Orthotopic liver transplantation is the only definitive treatment for patients with ALF.
    b. The advances in liver transplantation have improved ALF survival to greater than 60%.

H. Prognosis
  1. Predictive models of survival and need for liver transplantation are useful to identify the patients most likely to benefit from liver transplantation.
  2. The most important predictor of outcome seems to be the cause of ALF. Transplant-free survival is 50% or greater when acetaminophen, hepatitis A, acute ischemic injury, or pregnancy is the cause, whereas other causes confer less than 25% transplant-free survival. In addition, transplant-free survival is significantly decreased when patients present with grade III or grade IV encephalopathy compared with grade I or grade II encephalopathy.
  3. King's College criteria, developed from a cohort of about 600 patients with ALF, incorporate parameters such as cause of ALF and clinical parameters, including degree of encephalopathy and liver function tests, in order to evaluate the decision to perform transplantation versus provide medical therapy.
  4. MELD score may also be used for prognostication. Patients meeting King's College criteria or MELD score greater than 25 are at high risk of poor outcomes.

II. ACUTE PANCREATITIS

A. Epidemiology
  1. AP is responsible for 275,000 hospitalizations per year in the United States.
  2. In 2012, AP was the third most common gastroenterology diagnosis in the United States, with an annual cost of $2.6 billion.
  3. Incidence is estimated at 5–30 cases per 100,000.
  4. AP is classified according to disease severity. Overall, about 20% of patients with AP have a severe course with an overall mortality rate of approximately 5%.

B. Definitions
  1. The clinical diagnosis of AP is based on characteristic symptoms (i.e., abdominal pain and nausea), together with elevated serum concentrations of pancreatic enzymes. According to the Acute Pancreatitis Classification Working Group definition, two of the following three criteria must be met for a patient to be given a diagnosis of AP:
    a. Abdominal pain consistent with AP. This is typically persistent epigastric pain, sometimes radiating to the back.
    b. Serum lipase (or amylase) concentrations greater than 3 times the upper limit of normal
    c. Imaging CT, magnetic resonance imaging [MRI], or transabdominal ultrasonography) consistent with pancreatitis
  2. AP is classified according to disease severity as mild, moderately severe, or severe.
    a. Mild AP: Tends to be self-limiting with no organ failure or necrosis. There is also the absence of local and systemic complications.

    b. Moderately severe AP: Characterized by local complications and organ failure that lasts less than 48 hours. Local complications for moderately severe AP resolve without intervention.
    c. Severe AP: Characterized by persistent organ failure for more than 48 hours. Patients with severe AP usually have one or more local complications. Mortality rates are highest for severe AP (up to 20% of cases), particularly if persistent organ failure develops within the first few days of disease.
3. AP is further classified according to the phase. There are two distinct phases in this disease: early and late. The early phase usually lasts for the first week, and the late phase can last for weeks to months:
    a. Early: Symptoms of SIRS (e.g., temperature greater than 38°C or less than 36°C, heart rate greater than 90 beats/minute, respiratory rate greater than 20 breaths/minute or $Paco_2$ greater than or equal to 32 mm Hg or ventilator use, WBC greater than 12,000 or less than 4,000) with or without transient organ failure during the first week. Inflammatory responses and organ failure are mainly because of a response to local pancreatic injury.
    b. Late: Complications that occur after 1 week that can last weeks to months. This phase is characterized by persistent organ failure and the presence of local complications. The late phase occurs only in those with moderately severe or severe AP.
4. Local complications with moderately severe and severe AP may include:
    a. Peripancreatic fluid collections
    b. Pancreatic and peripancreatic necrosis (sterile or infected). Pancreatic necrosis is an area of nonviable pancreatic parenchyma identified by lack of enhancement on imaging, generally involving greater than 30% of the pancreas.
    c. Pseudocysts
    d. Walled-off necrosis (sterile or infected)
5. Organ failure associated with AP is typically cardiovascular, respiratory, or renal dysfunction. The modified Marshall scoring system is recommended to identify patients with AP with organ failure. A score of 2 or more for one of these three systems indicates organ failure.

C. Pathophysiology – AP is primarily caused by inappropriate activation of trypsinogen to trypsin. Trypsin is the key enzyme responsible for the activation of pancreatic zymogens. When trypsin is inappropriately formed and retained in the pancreas, activation of digestive enzymes inside the pancreas causes pancreatic autodigestion and pancreatic injury.

D. Causes
1. Gallstones
    a. Gallstone pancreatitis is the main cause of AP, responsible for 40%–70% of cases; 3%–7% of patients with gallstones develop pancreatitis.
    b. Gallstone pancreatitis occurs primarily in white women older than 60 years and in patients with small stones (less than 5 mm in diameter).
    c. Gallstone pancreatitis is usually an acute event that resolves once the gallstone has been removed or has passed.
    d. Patients may undergo a cholecystectomy to prevent further episodes in the future.
2. Alcohol use
    a. Excessive alcohol use is the etiology of pancreatitis in 25%–35% of cases.
    b. Symptoms can occur as an acute episode or present as a chronic pancreatitis.
    c. Alcohol-induced pancreatitis is more common in men than in women.
    d. Alcohol use and its association with pancreatitis is thought to have a dose-dependent relationship. Alcohol intake for more than 5 years or greater than 50 g daily increases the risk of pancreatitis. However, only about 5% of patients with a history of heavy alcohol consumption develop AP.

3. Hypertriglyceridemia
    a. Primary and secondary hypertriglyceridemia are increasingly recognized as causes of AP (5%–22% reported).
    b. If serum triglycerides are greater than 1000 mg/dL, hypertriglyceridemia should be suspected as the cause.
4. Certain medications can cause pancreatitis through varied mechanisms. Drug-induced pancreatitis is classified based on level of evidence and number of cases reported (Class 1, high level of evidence, through Class 4, very low quality of evidence). Examples include:
    a. Angiotensin-converting enzyme (ACE) inhibitors (Class 2)
    b. Azathioprine, 6-mercaptopurine (Class 1)
    c. HAART (highly active antiretroviral therapy) medications (e.g., didanosine) (Class 1, didanosine)
    d. DPP4 inhibitors, GLP1 agonists (Class 2)
    e. Valproic acid (Class 2)
    f. Propofol (Class 4)
5. Malignancy – The presence of a pancreatic tumor blocking the main pancreatic duct should be suspected in any patient older than 40 years with signs and symptoms of pancreatitis and no other apparent cause.
6. About 20% of AP cases are idiopathic.

E. Diagnosis
1. Signs and symptoms
    a. Abdominal pain
        i. AP pain is usually located in the epigastric region or left upper quadrant; however, it may radiate to the back, chest, or flank. Pain is typically constant and severe.
        ii. Gallstone pancreatitis–induced pain has been described as knifelike.
    b. Nausea
2. Laboratory abnormalities
    a. According to the Acute Pancreatitis Classification Working Group definition of AP, serum lipase (or amylase) concentrations at least 3 times the upper limit of normal are required for diagnosis.
    b. Serum lipase is preferred for diagnosis because elevations in serum lipase concentrations are more specific to the diagnosis of AP than elevations in amylase and serum lipase concentrations remain elevated longer than amylase concentrations.
        i. Amylase concentrations rise quickly (within a few hours) in AP; however, they return to normal within a few days.
        ii. Amylase concentrations may remain normal in alcohol-induced AP and hypertriglyceridemia.
3. Imaging
    a. Transabdominal ultrasonography should be done to confirm the diagnosis of AP for all patients.
    b. Contrast-enhanced CT scans of the abdomen are more than 90% sensitive and specific in diagnosing AP; however, routine use is unnecessary.
    c. Contrast-enhanced CT and/or MRI should be used in patients with an unclear diagnosis or in patients who do not improve after 48–72 hours to evaluate for complications.

F. Management
1. Hydration
    a. Patients with AP need early aggressive volume resuscitation because they are volume depleted for many reasons, including vomiting, reduced oral intake, third spacing of fluids because of inflammatory response, and diaphoresis. In fact, it has been hypothesized that worsening pancreatic hypoperfusion that develops from pancreatic inflammation in the setting of volume depletion leads to pancreatic necrosis. Thus, early aggressive volume resuscitation may prevent the development of pancreatic necrosis.

- b. Early aggressive volume resuscitation (i.e., within the first 24 hours) has been shown to be more effective than later aggressive volume resuscitation. Studies that have continuously used aggressive hydration strategies beyond the first 24 hours of presentation of AP have not shown benefit.
  - i. Although early aggressive volume resuscitation is recommended by the guidelines, this approach is defined in several different ways, including either 5–10 mL/kg/hr or 250–500 mL/hr for the first 12– 24 hours. In addition, the 2018 American Gastroenterological Association (AGA) guidelines suggest using either noninvasive (e.g., heart rate, mean arterial pressure, urine output) or invasive measures (e.g., stroke volume variation) to determine fluid responsiveness.
  - ii. A 2022 randomized controlled trial compared aggressive fluid resuscitation (defined as 20 mL/kg bolus followed by 3 mL/kg/hr) with moderate fluid resuscitation (defined as 1.5 mL/kg/hr for all patients, with hypovolemic patients receiving an initial 10 mL/kg bolus). Of note, all study patients were diagnosed with acute pancreatitis, and the outcome was progression to moderately severe or severe pancreatitis. The study was stopped early, however, because of increased harm in patients who received aggressive resuscitation, primarily fluid overload (20.5% vs. 6.3%; p=0.004) without any differences in efficacy outcomes. This finding suggests that less aggressive fluid strategies may be warranted, particularly for patients who present with less severe pancreatitis. However, in patients who present with severe AP, more rapid initial aggressive volume resuscitation may still be warrented. The most recent 2024 ACG guidelines for treatment of AP recommend fluid resuscitation, in line with the fluid management strategy, in line with the “moderate fluid resuscitation” arm of this study.
- c. Selection of intravenous fluid for initial volume resuscitation in AP may be important, favoring pH-balanced fluids. Low pH activates trypsinogen, implying that low-pH fluids exacerbate inflammatory response in AP. In a randomized controlled trial comparing initial resuscitation (within the first 24 hours) with lactated Ringer solution to 0.9% sodium chloride for patients with AP, there was a significant reduction in SIRS after 24 hours in patients resuscitated with lactated Ringer compared with 0.9% sodium chloride (84% reduction vs. 0%, respectively, p=0.035). The study also showed a significant reduction in C-reactive protein concentrations with administration of lactated Ringer solution compared with 0.9% sodium chloride. However, two recent randomized controlled trials comparing resuscitation with lactated Ringer solution and 0.9% sodium chloride showed similar early (within first 24 hours) reductions in SIRS with lactated Ringer solution, but no differences in SIRS prevalence after 24 hours or clinical outcomes, including mortality. Thus, because no study has shown meaningful clinical differences in fluid selection, the 2018 AGA guidelines make no recommendation on intravenous fluid of choice. However, the more recent 2024 ACG guidelines suggest lactated Ringer solution as the resuscitation of choice in AP.
- d. Because there can be harm in over-resuscitating patients, especially those with concomitant cardiovascular or renal failure, aggressive hydration may not be beneficial if there is no response within the first 6–12 hours.

2. Etiology-specific treatments
   - a. Insulin for hypertriglyceridemia-induced AP
     - i. High-dose insulin infusion is the treatment mainstay for severe AP secondary to hypertriglyceridemia.
     - ii. Insulin is initiated at 0.1 units/kg/hour, with dose adjusted on the basis of serum triglyceride concentrations, which are typically checked every 12 hours. If serum triglycerides do not decrease by at least 25%–50% in 24 hours, the insulin infusion is increased by 0.05 units/kg/hour until the goal serum triglyceride is achieved (ideally less than 500 mg/dL).
     - iii. To prevent hypoglycemia with high-dose insulin, blood glucose (BG) should be monitored hourly, and a dextrose infusion should be initiated and adjusted to maintain the BG at around 150 mg/dL.

b. Endoscopic retrograde cholangiopancreatography (ERCP)
    i. Although many gallstones are passed through the duodenum and lost in the stool without causing harm to the patient, gallstones that are not cleared can cause an obstruction in some patients in either the biliary tree or the pancreatic duct, which can lead to severe AP or cholangitis.
    ii. An ERCP, together with a sphincterotomy, may be used to extract gallstones from the pancreatic ducts or biliary tree.
    iii. There is considerable risk with ERCP, including bleeding and the potential to worsen AP because of manipulation of the pancreas. Because of this risk, the most recent 2024 ACG guidelines suggest medical therapy over early ERCP in patients with acute biliary pancreatitis without cholangitis.
    iv. Eight randomized controlled trials have evaluated the effectiveness of early ERCP in reducing the risk of complications in patients with gallstone AP. A limitation of these studies is that many did not exclude acute cholangitis, which is an indication for ERCP without AP. A systematic review controlling for patients with cholangitis found no benefit of early ERCP (mortality OR 0.67; 95% CI, 0.26–1.75).
    v. AP is the most common complication of ERCP. Although the incidence of post-ERCP pancreatitis has decreased significantly during the past few decades, post-ERCP pancreatitis continues to occur in 2%–4% of patients.
        (a) Rectal NSAIDs (i.e., 100 mg of indomethacin) after an ERCP can be given to patients at high risk of post-ERCP pancreatitis.
        (b) In a multicenter randomized controlled trial of 600 high-risk patients undergoing ERCP, 100 mg of rectal indomethacin (administered as two 50-mg suppositories given immediately post-ERCP) reduced the incidence of AP compared with placebo (9.2% vs. 16.9%, p=0.005) and, specifically, the development of moderate to severe AP (4.4% vs. 8.8%, p=0.03).

3. Infection
    a. Pancreatic and non-pancreatic infections contribute to mortality in patients with AP. The primary infectious concern with AP is infected necrotizing pancreatitis, which confers a high mortality rate (about 30%); thus, patients with severe acute necrotizing pancreatitis are at highest risk of pancreatic infections.
    b. The role of prophylactic antibiotics is controversial in AP.
        i. Early randomized trials showed a potential benefit in the reduction of infectious complications, particularly central line–related bloodstream infections, pulmonary infections, urinary infections, and pancreatic infections; however, the studies were unblinded, and the benefit was mostly confined to patients with severe AP.
        ii. In more recent literature with higher-quality trials, the benefit of prophylactic antibiotic is unsupported. A systematic review of 10 randomized controlled trials showed a trend toward reduced mortality with prophylactic antibiotics (OR 0.66; 95% CI, 0.42–1.04); however, the mortality benefit was lost among the subgroup of recent studies (after 2002: OR 0.85; 95% CI, 0.52–1.80). Similarly, there was no difference in risk of infected necrosis in more recent trials (OR 0.81; 95% CI, 0.44–1.49).
    c. According to the available information, use of prophylactic antibiotics to prevent the development of infected pancreatic necrosis is not recommended at this time.
    d. For patients who have not improved after 7–10 days of hospitalization with pancreatic necrosis, an infection should be suspected, and empiric antibiotics should be initiated at that time. Because of penetration issues, carbapenems, fluoroquinolones, metronidazole, or high-dose cephalosporins may be preferred; however, guidelines now also recommend piperacillin-tazobactam for severe AP, despite intermediate penetration..

4. Nutrition
   a. Historically, patients were kept NPO in order to rest the pancreas and prevent the further release of pancreatic enzymes. Patients were given TPN until complete resolution of AP.
      i. This practice has largely fallen out of favor because several studies have shown that early (within 24–48 hours) enteral nutrition is safe and effective for patients with AP. In addition, a recent meta-analysis of 11 randomized trials concluded that early (within 24–48 hours) feedings were not associated with increased adverse effects and may reduce hospital length of stay, particularly for mild to moderate AP. Enteral feeding maintains the gut mucosal barrier and helps prevent infectious complications such as infected necrosis, which may result from bacterial translocation from the gut.
      ii. A meta-analysis of eight trials comparing enteral nutrition with TPN in patients with AP showed decreased mortality (relative risk [RR] 0.5; 95% CI, 0.28–0.91), infectious complications (RR 0.39; 95% CI, 0.23–0.65), multiorgan failure (RR 0.55; 95% CI, 0.37–0.81), and surgical interventions (RR 0.44; 95% CI, 0.29–0.67) with the use of enteral nutrition. Enteral nutrition in these trials was given by the NJ route.
      iii. TPN is mainly reserved for patients unable to meet caloric demands with enteral feeding.
   b. Although the NJ route for enteral feeding has been preferred because it avoids the gastric area where pancreatic enzyme stimulation may occur, the NG route appears to be safe.
      i. A recent meta-analysis of three randomized controlled trials showed no significant differences in mortality, tracheal aspiration, or proportion meeting energy balance between the two routes; however, the results were limited by small sample sizes.
      ii. NG feeding is easier than NJ feeding because NJ tubes can be difficult to place, expensive, and inconvenient. However, there is concern that NG feeding may increase the risk of aspiration pneumonitis, particularly in patients with a history of aspiration.
5. Surgery
   a. Cholecystectomy should be performed in patients with gallstones retained in the gallbladder to prevent the recurrence of AP. For necrotizing biliary AP, cholecystectomy should be delayed until inflammation is resolved and fluid collections are cleared in order to avoid infection.
   b. Surgery is generally unnecessary for asymptomatic patients with pseudocysts and pancreatic or extrapancreatic necrosis.
   c. Surgical debridement of sterile necrosis is only necessary if gastric outlet obstruction or bile duct obstruction is present.
   d. Surgical intervention is the treatment of choice for infected necrotizing pancreatitis.
      i. For stable patients with infected necrotizing pancreatitis, surgical debridement should be delayed for at least 4 weeks to allow appropriate delineation of necrotic versus non-necrotic tissue, and antibiotics should be tried before surgical intervention.
      ii. Unstable patients with infected necrosis should undergo immediate debridement, and necrosectomy may be required in patients who do not respond to a combination of antibiotics and debridement.

Patient Case

3. A 44-year-old woman presents to the ED with a 2-day history of diffuse abdominal pain. Amylase is 700 IU/L, and lipase is 800 IU/L. She is given intravenous fluids with lactated Ringer solution and enteral nutrition through an NJ tube. However, after 48 hours, she has still not improved, and CT imaging reveals pancreatic necrosis involving 40% of the pancreas. Which interventions would best be performed at this time?
   A. Piperacillin/tazobactam should be prophylactically administered to prevent infected necrotizing pancreatitis.
   B. Surgical management of necrotizing pancreatitis is necessary.
   C. Antibiotics should be deferred unless systemic signs of infection are present.
   D. Meropenem should be prophylactically administered to prevent infected necrotizing pancreatitis.

III. GASTROINTESTINAL FISTULAS

A. Epidemiology
   1. About 20% of patients with Crohn disease will develop a spontaneous fistula in their lifetime, and up to 12% of patients with diverticulitis will develop a spontaneous fistula.
   2. Incidence of postoperative fistula formation varies from less than 1% to about 35%, depending on the type of abdominal surgery, with the rate of fistula increasing with more complex surgical procedures and more complicated resections/anastomoses. Additional factors such as Crohn's disease (incidence 15%–35%) increases the risk of fistula formation postoperatively.
   3. In the past 50 years, the mortality rate associated with fistulas has decreased significantly from greater than 40% to currently around 20%, mainly because of improvements in supportive care and the advent of nutritional support.
   4. GI fistulas remain a source of considerable morbidity with prolonged hospital courses, infections, and malnutrition.

B. Definition
   1. A fistula is any abnormal connection between two epithelialized surfaces. GI fistulas involve an abnormal connection between the GI tract and the skin, another internal organ, or an internal cavity such as the peritoneal or pleural space.
   2. Classification systems for fistulas:
      a. Anatomic: Describe the fistula origin and drainage point
         i. Internal: Connection to another internal organ or internal cavity (i.e., ileocolic)
         ii. External: Connection to the skin (i.e., enterocutaneous)
      b. Nomenclature: Typical method is from point of origin (e.g., gastro-, entero-, ileo-, etc.) followed by point of termination (e.g., -cutaneous, -colic, etc.).
      c. Physiologic: Classified according to daily fistula output. Daily fistula output is one of the most important determinants of morbidity and mortality, and it generally decreases before spontaneous closure.
         i. High output: Greater than 500 mL/day. High-output fistulas are associated with a mortality rate of about 35%.
         ii. Moderate output: 200–500 mL/day
         iii. Low output: Less than 200 mL/day

    d. Fistulas can also be described according to whether they maintain continuity with the GI tract.
        i. Lateral fistulas divert off the intestines while maintaining the continuity of the intestinal tract. With lateral fistulas, intestinal contents follow normal progression beyond the fistula.
        ii. End fistulas disrupt the continuity of the intestinal tract beyond the fistula.

C. Causes
1. Postoperative fistulas
    a. Most fistulas are formed after surgery (about 80%), most commonly after operations for cancer.
    b. Postoperative fistulas form because of either infection or breakdown at intestinal anastomoses.
    c. Postoperative fistulas are more commonly external, often because of the presence of a drain.
2. Spontaneous fistulas
    a. 15%–25% of GI fistulas occur spontaneously.
    b. Crohn disease and inflammatory bowel disease are the leading cause of spontaneous fistula formation, though pancreatitis and cancer (particularly if radiation therapy is involved) can also lead to spontaneous fistulas.
    c. Spontaneous fistulas often form because of local inflammatory processes that can cause local abscess formation or perforation.
    d. Spontaneous fistulas can be either external or internal.
3. Trauma-induced fistulas
    a. Some fistulas are caused by trauma (abdominal wounds or blunt trauma).
    b. Trauma may lead to fistula formation by causing vascular injury.

D. Diagnosis
1. Common presenting symptoms include pain, abdominal tenderness, leukocytosis, and fever. External fistulas are generally easier to recognize because of the presence of effluent at the drainage sites. Patients with internal fistulas may present with nonspecific symptoms such as diarrhea, dyspnea, or SIRS.
2. In postoperative patients, the first indication of a fistula is delayed recovery, which usually occurs within the first week after surgery.
3. Diagnostic workup should include fistula output volume, fistula output description (e.g., color, consistency), biochemical evaluation of fistula content (e.g., water-electrolyte balance, amylase, lipase, pH), microbiological evaluation of fistula content, and markers of nutritional status.
4. Radiographic contrast studies using CT or MRI are necessary to determine the anatomic aspects of the fistula (e.g., origin, length of fistula, presence of obstruction or abscesses). Barium is generally used for contrast because of its ability to show mucosal surfaces.

E. Treatment
1. Fluid resuscitation and electrolyte management
    a. GI fistula fluid is typically iso-osmotic and rich in sodium, potassium, chloride, and bicarbonate. High-output fistulas can result in large fluid and electrolyte imbalances leading to dehydration, hypokalemia, hyponatremia, and metabolic acidosis.
    b. Fistula output from the upper GI tract is generally more acidic and rich in potassium. Replacement fluid should include a maintenance infusion of 0.9% sodium chloride with potassium and frequent reassessments for potassium corrections.
    c. Pancreatic and duodenal fistulas result in bicarbonate losses and may require bicarbonate replacement.
    d. Fistula fluid composition may be analyzed in order to correctly replete fluid and electrolyte deficits.

2. Drainage
   a. Drainage is used to prevent the accumulation of fluid and the development of infection.
   b. Most enterocutaneous fistulas will drain to skin spontaneously; however, some fluid may be retained in the fistula tract, which may lead to infection.
   c. Vacuum-assisted closure (VAC) devices administer negative pressure wound therapy and can increase blood flow and decrease fluid collections. For enterocutaneous fistulas, a VAC system can help protect skin and decrease fistula output.
3. Nutrition
   a. Nutritional deficiencies are present in 55%–90% of patients with GI fistulas, particularly with upper GI fistulas, because there is substantial fluid, electrolyte, and protein loss from the upper GI tract.
   b. Because of nutritional deficits, patients may need nutritional supplementation in excess of daily demands. Patients with low-output fistulas may need additional protein, and patients with high-output fistulas may need additional daily caloric and protein requirements (e.g., 1.5–2 times basal daily expenditure).
   c. Enteral feedings are the preferred method for nutritional supplementation because enteral feedings provide direct stimulation to the enterocyte, which may enhance mucosal proliferation.
      i. In a retrospective cohort study of 335 patients with high-output small intestine fistulas (median output 1350 mL/day), 85% (n=285) were treated with enteral nutrition. Spontaneous closure rates were acceptable.
      ii. Tolerability may limit the use of enteral feeding (e.g., high gastric residuals, diarrhea).
   d. TPN has the potential advantage of improving spontaneous closure rates because of reductions in GI secretions and reduction in fistula output volumes, particularly for patients with high-output fistulas and when combined with antisecretory agents (e.g., octreotide).
   e. Fistula site may also influence the choice of enteral nutrition compared with TPN. In general, enteral feeding is provided for fistulas from the esophagus, lower small intestine, and colon, whereas TPN is used for fistulas from the stomach, pancreas, or upper small intestine.
   f. Some evidence supports adding supplements to enteral feeding. These include fish oil, omega-3 fatty acids, and glutamine, which may improve immune function or increase blood flow to the intestinal tissue. In a study of 28 patients with high-output fistulas, patients who received glutamine supplementation (0.3 g/kg/day orally) in addition to TPN were significantly more likely to have spontaneous fistula closure.
4. Somatostatin and octreotide
   a. Somatostatin is a tetradecapeptide that is naturally found in the GI tract and the nervous system.
      i. It has several biological effects, including inhibition of hormone secretion (i.e., gastrin, cholecystokinin, secretin, insulin, glucagon), inhibition of exocrine secretory response (i.e., gastric acid and pancreatic secretion), inhibition of motor activity in the GI tract, inhibition of nutrient absorption, and stimulation of water and electrolyte absorption.
      ii. Octreotide is an octapeptide synthetic analog of somatostatin with similar activity.
      iii. Because output volume is correlated with spontaneous closure, drugs such as somatostatin and octreotide are used to reduce output volumes.
   b. Somatostatin vs. octreotide
      i. Somatostatin has a very short half-life (about 1–2 minutes), which requires a continuous infusion, whereas octreotide has a half-life of around 2 hours, allowing for intermittent dosing (e.g., three times daily).
      ii. Effect of octreotide appears to diminish with repeated dosing, possibly because of down-regulation of somatostatin receptors.
      iii. Somatostatin is active at all somatostatin receptors, whereas octreotide has variable affinity at the somatostatin receptors.

   c. Somatostatin significantly reduces output volumes. One prospective, randomized controlled single-center trial compared somatostatin 250 mcg/hour intravenously continuously with placebo for patients receiving TPN. Somatostatin significantly reduced the time to achieve a 50%, 75%, and 100% reduction in fistula output compared with placebo; also, although there was no difference in the rates of fistula closure (85% vs. 81.25%), the time to fistula closure was significantly reduced with the use of somatostatin (13.9 days vs. 20.4 days, $p<0.05$).
   d. Octreotide has been shown to decrease fistula output in some studies, though in other trials, it had no effect on fistula output.
      i. One small study of 14 patients showed a beneficial effect of octreotide on output volumes. In this crossover study, octreotide at 100 mcg subcutaneously three times daily significantly reduced fistula output compared with placebo for the first 2 days of therapy by about 400 mL/day. When the group that was originally randomized to receive octreotide crossed over to the placebo arm, output increased by about 250 mL/day.
      ii. Two subsequent studies did not show similar results on fistula output. Possible reasons for decreased efficacy with octreotide include diminished response with repeat dosing and decreased activity at some somatostatin receptors.
   e. Reduction in fistula output with the use of somatostatin or octreotide should occur within 48 hours. If no noticeable response in fistula response occurs at 48 hours, treatment should be discontinued.

5. Refractory high-output fistula management
   a. Acid-suppressing medications (e.g., PPIs and histamine-2 receptor antagonists) have been studied for the treatment of refractory fistula because of their ability to decrease gastric acidity and decrease the amount of gastric secretions. Proton pump inhibitors are more effective than histamine-2 receptor antagonists for refractory fistula output.
   b. Antimotility agents are usually recommended (e.g., loperamide, diphenoxylate/atropine, codeine) because of their ability to inhibit the activity of gastrointestinal tract muscles.
      i. Loperamide has the greatest effect on fistula output. In studies, loperamide doses up to 12–24 mg per dose have been given safely for the management of high-output fistulas. However, due to concerns for adverse reactions, caution should be advised with doses higher than 16 mg per day. Additionally, administration of large quantities of the liquid form of loperamide may increase fistula output.
6. Conservative versus surgical management
   a. Conservative management is first line for most patients, with the primary goal being spontaneous closure of the fistula. Several prognostic indicators improve the likelihood of spontaneous closure.
      i. Low-output fistulas
      ii. Patients younger than 40 years
      iii. Fistula sites: Oropharyngeal, esophageal, duodenal, pancreatic, jejunal
      iv. A long fistula tract (greater than 2 cm)
      v. Intestinal continuity maintained
   b. Surgery is usually indicated for fistulas that fail to close spontaneously after 30–60 days. Some causes of fistula formation (e.g., bowel injury caused by trauma or certain surgical procedures) may require emergency surgery to repair damage.

Patient Case

4. A 34-year-old woman with morbid obesity presents to the surgical ICU after gastric bypass surgery 1 week prior with an enterocutaneous fistula requiring medical management. Her current output is about 600 mL/day. For the patient's high-output fistula, which best represents the intervention that has not been associated with a reduction in fistula output volume?
   - A. Somatostatin 250 mcg/hour intravenously continuously.
   - B. Octreotide 100 mcg subcutaneously three times daily.
   - C. TPN.
   - D. Glutamine 0.3 g/kg/day orally.

IV. POSTOPERATIVE ILEUS

A. Epidemiology
  1. Incidence of POI can vary, depending on the type of procedure:
     a. Abdominal hysterectomy: About 3%
     b. Bowel resection: About 15%
  2. POI can lead to a prolonged hospital stay, prolonged recovery, and increased morbidity including increased postoperative pain, PONV, and risk of postoperative complications (e.g., aspiration pneumonia, thromboembolism, nosocomial infection).

B. Definition
  1. POI is a transient impairment of appropriate GI motility after a surgical procedure.
  2. The paralytic state in POI is not caused by a mechanical obstruction, and ileus can affect the stomach, small intestine, or large intestine.
  3. The duration of POI is typically 2–3 days after a procedure, but POI may last up to 6 days postoperatively. Return to normal bowel function is monitored using objective signs such as passing of flatus, active bowel sounds, or a bowel movement.
     a. The duration of POI often depends on the surgical site. Return to normal function is fastest for the small bowel, normally within 24 hours. Paralytic state may last on average 24–48 hours in the stomach, whereas it may take up to 3–5 days for the colon to return to normal function.
     b. If POI persists beyond about 6 days, it is called a paralytic ileus.

C. Causes
  1. Bowel motility is controlled by the autonomic nervous system. Parasympathetic stimulation increases bowel motility, whereas sympathetic stimulation inhibits it.
     a. Increased sympathetic output postoperatively may lead to increased ileus formation. The colon is more dependent on the autonomic nervous system than the stomach or small intestine, which may explain the longer recovery time postoperatively.
     b. The vagal nerve is important to parasympathetic activity in the stomach. Inadvertent damage to the vagal nerve during abdominal surgery can result in impaired emptying of the stomach.

2. During periods of fasting, upper GI tract motility is controlled by the migrating motor complex, which moves intestinal contents distally.
    a. During periods of fasting postoperatively, the contractility of the stomach and small intestine is entirely dependent on the migrating motor complex.
    b. Inflammation of the GI tract after surgery, inhibitory neural reflexes, and the release of inhibitory neurotransmitters such as nitrous oxide, substance P, and vasoactive intestinal peptide may lead to decreased activity of migrating motor complex.
3. Exacerbating factors
    a. Anesthesia: Delayed gastric emptying has been observed with the use of halothane, enflurane, and atropine.
    b. Postoperative opioids: Opioids, through agonism at the mu$_2$-opioid receptor, slow GI motility mainly by decreasing colonic motility. High doses and prolonged courses postoperatively can contribute to paralytic ileus.
    c. Other medications known to decrease GI motility are often given perioperatively (e.g., anticholinergics).

D. Diagnosis
1. POI is typically characterized by abdominal distension, lack of bowel sounds, delayed passage of flatus or stool, and accumulation of gas and stool in the bowels, which may lead to nausea and vomiting.
2. All patients should have a physical examination for abdominal distension, followed by plain abdominal radiographs to identify air and dilated loops of bowel.
3. An abdominal CT scan can be used to rule out a mechanical obstruction.

E. Management
1. Use of epidural anesthesia
    a. Epidural blockade may improve POI by reducing local sympathetic and inflammatory response postoperatively and increasing splanchnic blood flow. It may also reduce postoperative opioid use.
    b. Several studies of epidural anesthesia have shown reductions in POI. Most studies that showed benefit used thoracic epidural blockade and administered epidural anesthesia for at least 48–72 hours.
2. Use of laparoscopic surgery: Few studies have shown reduced POI rates with laparoscopic surgery compared with open abdominal procedures. However, studies have shown reductions in inflammatory response (e.g., cytokine production) and reduced postoperative pain with laparoscopic procedures, which may affect POI.
3. NG decompression
    a. Historically, NG tubes were placed in most patients for gastric decompression and used until normal GI function returned.
    b. In a meta-analysis of 26 trials including 4000 patients, the use of NG tube insertion was routinely associated with fever, atelectasis, and pneumonia, though patients treated without NG tubes did have more abdominal pain and vomiting. The study concluded that for every patient who required NG tube insertion, 20 patients could be treated effectively without NG tube insertion and that NG tubes should be used selectively because of concerns for adverse effects.
4. Enteral feeding
    a. Traditionally, enteral feeds were delayed postoperatively until after ileus was resolved.
    b. Recent data from several randomized controlled trials show a modest improvement in POI resolution from early enteral feedings, typically initiated within the first 24 hours postoperatively. This effect probably results from stimulation of the bowel.

5. Sham feeding
    a. Sham feeding is the process of eliciting the release of hormonal and neuronal GI activity without regular feeding. One way by which this mechanism can occur is through the chewing of gum.
    b. In a small randomized study of 19 patients, chewing gum three times a day reduced time to first flatus (2.1 days vs. 3.2 days, $p<0.01$) and time to first defecation (3.1 days vs. 5.8 days, $p<0.01$) compared with control.
6. Pharmacologic therapy
    a. Opioid-sparing analgesia
        i. NSAIDs have two potential effects on resolving POI: sparing opioids through their analgesic effects and reducing the production of inflammatory mediators (e.g., prostaglandin). Adding an NSAID to opioid therapy reduces the need for opioids by 20%–30%.
        ii. A randomized, double-blind study of morphine patient-controlled analgesia with or without ketorolac showed decreased morphine use and earlier first bowel movements (1.5 days vs. 1.7 days, $p<0.05$) in the patients who received the additional ketorolac compared with those who did not.
        iii. Use should be carefully assessed so that the benefit outweighs the risk of postoperative bleeding caused by platelet inhibition together with the potential increased risk of anastomotic leak and wound dehiscence.
    b. Prokinetics and laxatives
        i. Erythromycin
            (a) Erythromycin is a macrolide antibiotic that has prokinetic activity as a motilin receptor agonist. Motilin induces gastric contractions and migrating motor complex.
            (b) In randomized controlled trials, erythromycin does not appear beneficial for POI resolution.
        ii. Metoclopramide. No studies of POI have shown a benefit; however, the antiemetic activity of metoclopramide may be beneficial as an adjunctive therapy for patients with POI.
        iii. Laxatives
            (a) Laxatives should play an important role in the management of POI because of their stimulatory action in the GI tract; however, data are limited on the use of laxatives.
            (b) Most of the data regarding the use of laxatives for POI support the use of bisacodyl suppositories (e.g., 10 mg rectally daily), which have reduced time to return of normal bowel function and some evidence of reduced hospital length of stay.
        iv. Gastrografin
            (a) Gastrografin is an oral contrast agent with theoretical benefit in POI because it is hypertonic and reduces gut wall edema by drawing fluid into the gut lumen and promoting peristalsis.
            (b) In a randomized controlled trial of 80 patients with prolonged POI, gastrografin did not significantly reduce the mean duration of POI compared with placebo (83.7 vs. 101.3 hours, $p=0.19$).
    c. Peripherally acting mu-opioid receptor antagonists
        i. Alvimopan (Entereg)
            (a) Alvimopan has 200-fold selectivity for the peripheral opioid receptors and has poor absorption from the GI tract when administered orally (bioavailability about 6%), decreasing the likelihood of systemic absorption and penetration across the blood-brain barrier.

- (b) Alvimopan was studied in four North American phase III randomized controlled trials for POI. Each trial included adult surgical patients (generally bowel resection and abdominal hysterectomy) who received standard postoperative care for prevention of POI. In all four trials, patients were randomized to receive placebo, alvimopan 6 mg orally twice daily, or alvimopan 12 mg orally twice daily beginning immediately before surgery and continuing for 7 days (total of 15 doses).
  - (1) Three of the four trials showed significant reductions in time to return of normal bowel function (i.e., tolerating solid food and passing bowel movements). The 12-mg dose was especially beneficial in females and patients older than 65.
  - (2) A pooled analysis from the four phase III trials comparing outcomes in patients who received the 12-mg dose versus placebo showed a 20-hour reduction in time to return of normal bowel function (102 hours vs. 121.8 hours, $p<0.05$) and a reduction in hospital length of stay (6.6 days vs. 7.6 days, $p<0.001$).
- (c) Alvimopan was also associated with significantly less POI-related morbidity, including NG tube insertion (6.6% vs. 11.5%, $p<0.001$), and fewer POI complications, including paralytic ileus, as well as adverse events of nausea, vomiting, and abdominal distension (2.9% vs. 8.8%, $p<0.001$).
- (d) In a 12-month study of alvimopan for opioid-induced bowel dysfunction in patients with chronic non-cancer pain, myocardial infarction rates were higher in patients treated with alvimopan than in placebo (7 [1.3%] vs. 0 [0%]).
  - (1) This higher risk did not appear to be related to the therapy duration (12 months). In addition, increased risk of cardiovascular events has not occurred in other alvimopan studies, including POI studies, and no causal relationship has been established.
  - (2) However, given the concern of added risk, the FDA has since developed REMS (Risk Evaluation and Mitigation Strategies) for the use of alvimopan. Hospitals that intend to use alvimopan should be enrolled in the EASE (ENTEREG Access Support & Education) program. The EASE program limits the use of alvimopan to short-term inpatient use, and patients cannot receive more than 15 doses.

ii. Methylnaltrexone
- (a) Methylnaltrexone is a peripherally acting mu-opioid receptor antagonist approved for treatment of chronic opioid-induced constipation. Methylnaltrexone is not FDA approved for the treatment of POI.
- (b) Methylnaltrexone is typically given subcutaneously daily or every other day for opioid-induced constipation in a weight-based dose of 0.15 mg/kg rounded to the nearest 2 mg (usually 8 or 12 mg)
- (c) Results from phase III trials showed no reduction in duration of POI compared with placebo, but methylnaltrexone may be an alternative to alvimopan if oral therapy is not an option.

iii. Naloxegol
- (a) Naloxegol is another oral peripherally acting mu-opioid receptor antagonist, which is approved for opioid-induced constipation. Dosing for opioid-induced constipation is 25 mg orally once daily, with dosing reductions required for renal dysfunction and concomitant CYP3A4 inhibitors.
- (b) Like methylnaltrexone, naloxegol is not FDA approved for the treatment of POI.

Patient Case

5. A 40-year-old man presents for a large bowel resection. Because of the complexity of the procedure and the anticipated use of perioperative opioids and inhalation anesthesia, the team is creating a plan to prevent POI. Which medication would be best to recommend for reducing the incidence of POI?
   - A. Hydromorphone patient-controlled analgesia postoperatively instead of morphine.
   - B. Alvimopan 12 mg orally just before surgery and continued twice daily for 7 days.
   - C. Metoclopramide 5 mg intravenously every 6 hours for 7 days postoperatively.
   - D. Octreotide 100 mcg subcutaneously every 8 hours for 7 days postoperatively.

V. POSTOPERATIVE NAUSEA AND VOMITING

A. Epidemiology
   1. Postoperative vomiting occurs in about 30% of overall surgical patients, whereas postoperative nausea occurs in about 50%. In high-risk patients, the incidence of PONV can be as high as 80%.
   2. Uncontrolled PONV may result in a prolonged stay in the post-anesthesia care unit and, sometimes, unplanned hospital admissions for outpatient procedures.

B. Risk Factors
   1. Surgical factors that increase the risk of PONV:
      a. Use of volatile anesthetics: The effect of volatile anesthetics on PONV is usually dose-dependent and typically presents within the first 6 hours postoperatively.
      b. Use of postoperative opioids: The effect of postoperative opioids similarly increases the risk of PONV in a dose-dependent fashion.
      c. Use of general anesthesia
      d. Duration of anesthesia: Each 1-hour increase in duration of anesthesia increases the risk of PONV.
      e. Type of surgery: Cholecystectomy, laparoscopic, gynecological are most commonly associated with PONV.
   2. Patient-specific factors that increase the risk of PONV:
      a. Female sex
      b. History of motion sickness, chemotherapy-induced nausea and vomiting, or PONV
      c. Nonsmoker
      d. Younger age
   3. The Apfel simplified risk score is based on four predictors: female sex, history of PONV and motion sickness, nonsmoking status, and use of postoperative opioids. The estimated risk of PONV is 10%, 20%, 40%, 60%, and 80% when zero, one, two, three, or four of the above risk factors are present, respectively.
   4. A stratified prevention strategy is suggested according to the number of risk factors, as follows:
      a. Low risk (zero risk factors): No pharmacologic prophylaxis recommended; a “wait and see” strategy is suggested
      b. Medium risk (one or two risk factors): One or two prophylactic interventions are recommended.
      c. High risk (more than two risk factors): Three or more prophylactic interventions should be used.
      d. Of note, new guidelines recommend that at least one pharmacologic prophylactic therapy be administered to all patients regardless of risk factors because risk scores are not completely predictive.

C. Prevention
   1. A multimodal strategy that usually targets risk avoidance should be implemented to avoid PONV. The IMPACT study enrolled more than 5000 surgical patients and evaluated six interventions for the prevention of PONV in a factorial design, including avoidance of volatile anesthetics and nitrous oxide, use of short-acting opioids in the postoperative period, and use of ondansetron, dexamethasone, and droperidol for pharmacologic prophylaxis. Each intervention except for choice of opioid was associated with a reduction in the incidence of PONV; however, the study showed that the interventions acted independently of each other, and thus, a benefit with several interventions was seen.
   2. Regional anesthetics should be used instead of general anesthetics, when possible, because general anesthetics are associated with an 11-fold increase in PONV. If general anesthesia is required, propofol is preferred to volatile anesthetics for inducing and maintaining anesthesia. In the IMPACT study, the use of propofol compared with volatile anesthetics was associated with a 19% relative risk reduction in the incidence of PONV ($p<0.001$).
   3. Avoiding nitrous oxide as a carrier gas is recommended; use of other carrier gases (e.g., nitrogen, oxygen) is associated with a 12% relative risk reduction in PONV ($p=0.003$).
   4. Perioperative opioid use should be minimized, if possible. Guidelines recommend the use of perioperative NSAIDs for opioid-sparing analgesia. Intravenous acetaminophen has also been studied as part of a multimodal analgesia strategy to reduce postoperative opioid use; although oral acetaminophen may also be used, its effect on PONV has not been well studied. According to data from the IMPACT study, which compared remifentanil with fentanyl, the use of short-acting opioids does not appear to be associated with the incidence of PONV.
   5. Pharmacologic prophylaxis:
      a. Serotonin-3 antagonists are first-line treatment for pharmacologic prophylaxis. These drugs are most effective for the prevention of PONV when given at the end of surgery.
         i. Ondansetron, when given at a prophylactic dose of 4 mg intravenously, has greater anti-vomiting effects (number needed to treat [NNT] = 6) than antinausea effects (NNT = 7).
         ii. Granisetron at doses of 0.35–3 mg intravenously is as effective as ondansetron, whereas palonosetron 0.075 mg intravenously was more effective than ondansetron at preventing PONV in a small study of gynecological laparoscopic surgical patients (42% PONV with palonosetron vs. 67% with ondansetron, $p<0.05$). Palonosetron is a second-generation serotonin-3 antagonist with longer half-life than other agents.
      b. Dexamethasone is most effective for the prevention of PONV when given at the time of induction.
         i. According to data from the IMPACT study, dexamethasone 4 mg intravenously was associated with a 26% relative risk reduction in the incidence of PONV.
         ii. A recent study evaluating a higher dexamethasone dose (e.g., 8 mg intravenously) at the time of induction for the prevention of PONV found that this high-dose strategy resulted in an 8% absolute risk reduction in vomiting compared with standard PONV care.
         iii. When used for PONV, dexamethasone may cause modest increases in blood glucose in patients both with or without diabetes.
      c. Droperidol at prophylactic doses of 0.625–1.25 mg intravenously is effective for the prevention of PONV when given at the end of surgery.
         i. Efficacy of droperidol is similar to that of ondansetron and dexamethasone, with a relative risk reduction of about 25% (data from the IMPACT study).
         ii. FDA black box warnings for cardiovascular risk with droperidol have limited its use; however, the doses used for preventing PONV are very low and are unlikely to be associated with cardiovascular effects.

d. Neurokinin-1 receptor antagonists (e.g., aprepitant) should be given at the time of induction. Data are limited on the use of neurokinin-1 receptor antagonists in PONV; however, they appear to be as effective as ondansetron. One large randomized double-blind trial evaluated 805 abdominal surgery patients who were randomly assigned to receive 40 mg of oral aprepitant, 125 mg of oral aprepitant, or 4 mg of intravenous ondansetron. Although there was no difference in the primary outcome of complete response (considered no vomiting or use of rescue therapy), aprepitant at both doses did reduce the occurrence of vomiting compared with ondansetron.

e. Transdermal scopolamine can be applied the evening before surgery. When used with ondansetron, adding scopolamine was associated with a 10% absolute reduction in the occurrence of PONV within the first 24 hours postoperatively.

D. Rescue Therapy
   1. When rescue therapy is needed within the first 6 hours postoperatively, an antiemetic should be selected from a therapeutic class different from the initial prophylactic drug. Repeat doses of the same drugs that were used for initial prophylaxis can be tried if PONV occurs more than 6 hours after surgery.
   2. If patients did not receive a prophylactic agent, rescue treatment with a serotonin-3 antagonist should be tried.

Patient Case

6. A 27-year-old woman presents for a total abdominal hysterectomy. She is a nonsmoker who has a significant history of motion sickness. During the procedure, she is expected to receive general anesthesia with volatile anesthetics. She will probably require high-dose opioids perioperatively. Given this patient's risk of developing PONV, which would she best receive for prevention of PONV?
   A. Patient has a high risk of PONV; she should receive transdermal scopolamine the evening before surgery, dexamethasone 4 mg intravenously at the time of induction, and ondansetron 4 mg intravenously at the end of surgery.
   B. Patient has a moderate risk of PONV; she should receive dexamethasone 4 mg intravenously at the time of induction and ondansetron 4 mg intravenously at the end of surgery.
   C. Patient has a high risk of PONV; she should receive dexamethasone 4 mg intravenously at the time of induction and ondansetron 4 mg intravenously at the end of surgery.
   D. Patient has a low risk of PONV; she should receive ondansetron 4 mg intravenously at the end of surgery.

VI. UPPER GASTROINTESTINAL BLEEDING

A. Definition and Epidemiology
   1. Bleeding that occurs in the esophagus, stomach, or duodenum
   2. In the United States, the annual incidence is 65 hospitalizations per 100,000 adults. Incidence is twice as high in males as in females and increases with age.
   3. Accounts for 350,000 hospitalizations per year at an annual cost of $2.5 billion
   4. UGIB is 4 times more common than lower GI bleeding, and the hospitalization rate is around 6-fold higher.

5. Mortality at 28 days after hospital admission for non-variceal hemorrhage is about 13%, whereas mortality after variceal hemorrhage is about 20%. Mortality rates after both UGIB classifications seem to be decreasing with advances in care.

B. Etiologies
  1. Nonvariceal hemorrhage
    a. Gastric and/or duodenal ulcer
      i. Most common cause of severe cases of UGIB, accounting for 47% of all UGIB episodes
      ii. Bleeding is more common in the setting of anticoagulant use and is typically self-limited.
      iii. Most commonly caused by an *H. pylori* infection, but may also be secondary to NSAIDs, hyperacidity (e.g., in Zollinger-Ellison syndrome), or stress-related mucosal disease (stress-related mucosal damage is discussed in detail in the Supportive and Preventive Medicine chapter)
    b. Esophagitis
      i. Noted in around 13% of patients with UGIB
      ii. Risk factors include history of gastroesophageal reflux disease, medication use (e.g., NSAIDs, oral bisphosphonates, tetracycline), and infection (e.g., *Candida*, herpes simplex virus).
      iii. Commonly presents with hematemesis and less commonly associated with melena
      iv. Lower rebleeding and mortality rate than other sources of UGIB
    c. Gastroduodenal erosions (erosive gastritis/duodenitis): Defects of the gastric/duodenal mucosal layer that lead to inflammation without ulcer formation
      i. Causes are similar to those for gastric/duodenal ulcers. Additional risk factors include excessive alcohol consumption, radiation injury, bariatric surgery, and chronic bile reflux.
      ii. Bleeding is more common in the setting of anticoagulant use and is typically self-limited.
      iii. May progress to ulcer formation
    d. Mallory-Weiss tear: A longitudinal mucosal laceration in the distal esophagus and proximal stomach (an intramural dissection)
      i. A sudden increase in intra-abdominal pressure leads to forceful distention of the gastroesophageal junction and a resultant mucosal tear.
      ii. Typically caused by forceful vomiting
    e. Less common causes: Vascular malformation, malignant formations, aortoenteric fistulas, gastric antral vascular ectasia, and prolapse gastropathy
  2. Variceal hemorrhage
    a. Relatively few severe cases of UGIB are secondary to variceal hemorrhage (< 5%), but the incidence is higher in patients with cirrhosis.
    b. Mortality rate is around 20% at 6 weeks.
    c. Portal hypertension caused by the obstruction of venous blood flow through the cirrhotic liver leads to increased pressure in the portal vein and causes the redirection of blood flow to other areas of the body.
    d. Varices may be present in any portion of the GI tract, but they are most common in the esophagus and stomach.
    e. Gastroesophageal varices are present in about 50% of patients with cirrhosis. About 12% of patients with varices will develop variceal hemorrhage within 1 year of diagnosis, and the recurrence rate for variceal hemorrhage within 1 year is about 60%.

C. Initial Assessment and Risk Stratification
  1. Most patients (50%) present with both melena and hematemesis; 30% have hematemesis (either red blood or “coffee-ground” emesis) alone, and 20% have melena alone.
  2. Hematochezia (bright red blood per rectum) may also be present (in about 5% of patients), which may represent a swift UGIB (about 1 L of blood is needed in the stomach to cause hematochezia, whereas only 50–100 mL is needed to cause melena).

3. Bleeding ulcers may result in right upper quadrant pain. Mallory-Weiss tears may present as emesis, retching, or coughing before hematemesis. Patients with symptoms associated with chronic liver disease will likely have variceal bleeding.
4. Hemodynamic instability may be present in patients with significant hypovolemia. Initial care of these patients should focus on patient stabilization.
5. Insertion of an NG tube is controversial because it has not been shown to improve clinical outcomes, but inspection of the aspirate may be useful in patients without frank hematemesis.
    a. If the aspirate contains bright red blood, urgent endoscopy is likely indicated.
    b. A normal-appearing aspirate does not rule out UGIB because about 15% of patients with a normal aspirate have high-risk lesions on endoscopy.
    c. Insertion of an NG tube may be contraindicated in patients with a history of varices, particularly those with recent endoscopic band ligation.
6. In patients with a variceal hemorrhage, a hepatic venous pressure gradient greater than 20 mm Hg is a strong predictor of early rebleeding and death and can be used for risk stratification. Measuring this gradient is not feasible at most centers, but more than 80% of patients with Child-Turcotte-Pugh class C have a gradient greater than 20 mm Hg.
7. Scoring tools may help in patient risk stratification, which can aid in site of care and endoscopy timing decisions.
    a. The Blatchford scoring system uses clinical and laboratory parameters to predict the need for clinical intervention.
    b. The Rockall scoring system incorporates endoscopic findings and predicts a patient’s risk of rebleeding and death.
    c. The AIMS65 scoring system uses clinical and laboratory parameters to estimate in-hospital mortality, hospital length of stay, and cost in patients with acute UGIB.
    d. Current guidelines recommend using a Blatchford score of 1 or less to identify patients at very low risk of rebleeding or mortality who may not require hospitalization or inpatient endoscopy. The guidelines do not make a recommendation for or against using the Rockall score and recommend against using the AIMS65 scoring system to identify patients at low risk of rebleeding or mortality.

D. Management
1. General measures
    a. Venous access with two large-caliber (at least 18 gauge; 16 gauge preferred if hemodynamically unstable) peripheral intravenous catheters should be achieved. Access by peripheral intravenous catheters is preferred to central venous catheterization because of their improved ability to deliver intravenous fluids more quickly (because of the Poiseuille law).
    b. Supplemental oxygen by nasal cannula should be administered to patients with an oxygen saturation below 90%.
    c. A blood type and cross-match should be sent immediately (in preparation for possible blood transfusion).
2. Hemodynamically unstable patients should be resuscitated immediately with intravenous fluids (crystalloids) and blood transfusions (if indicated).
    a. A study of patients with hemodynamic instability secondary to UGIB compared usual care with intensive resuscitation focused on achieving hemodynamic stability, a hematocrit greater than 28%, and an INR less than 1.8. Intensive resuscitation was associated with a lower mortality rate (2.8% vs. 11.1%, p=0.04) and a lower incidence of myocardial infarction (5.6% vs. 13.9%, p=0.04).
    b. See the Shock Syndromes II: Hypovolemic, Critical Bleeding, and Obstructive chapter for further discussion of hypovolemic shock secondary to hemorrhage.

3. Transfusion
    a. Current guidelines recommend a transfusion threshold of 7 g/dL for hospitalized hemodynamically stable patients, including those in the ICU, and a threshold of 8 g/dL in patients with preexisting cardiovascular disease. This recommendation does not extend to patients with acute coronary syndrome.
    b. A higher hemoglobin threshold may be appropriate in patients with hypotension or who are bleeding rapidly.
    c. Platelet transfusion, typically if the platelet count is less than 50,000/mm^3, should be considered.
4. Endoscopy
    a. Diagnostic endoscopy
        i. Used to diagnose and assess the risk posed by the bleeding lesion(s). Therapeutic endoscopy may also be used for the lesion(s) to reduce the risk of bleeding recurrence (discussed later in the chapter).
        ii. Patients with UGIB should generally have a diagnostic endoscopy within 24 hours.
        iii. Patients who are hemodynamically unstable and those with a suspected variceal UGIB should have a diagnostic endoscopy as soon as possible and no later than 12 hours after presentation.
        iv. Erythromycin or metoclopramide may be used when a large amount of blood in the stomach would hinder an endoscopy; however, routine use is not recommended. Use reduces the need for repeated endoscopy (OR 0.55; 95% CI, 0.32–0.94) but does not alter the need for blood products, length of hospital stay, or need for surgery.
        v. Endotracheal intubation before endoscopy may be indicated to prevent aspiration, but patient selection is controversial.
        vi. Endoscopic findings predict the risk of rebleeding and guide further therapies.
            (a) Nonvariceal UGIB: Stigmata of recent hemorrhage from a peptic ulcer predict the risk of further bleeding and guide management decisions (Table 6).

Table 6. Endoscopic Findings of Bleeding Peptic Ulcers, Prevalence, and Rebleeding Rate

Risk of Rebleeding	Stigmata of Recent Hemorrhage	Forrest Grade	Prevalence	Rebleeding Rate
High	Active spurting bleeding	IA	9.3% (spurting and oozing)	55% (spurting and oozing)
	Active oozing bleeding	IB		
	Nonbleeding visible vessel	IIA	6.1%	43%
	Adherent clot	IIB	6.5%	22%
Low	Flat pigmented spot	IIC	13.1%	10%
	Clean base	III	52.6%	5%

Information from: Laine L, Peterson W. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27; Enestvedt BK, Gralnek IM, Mattek N, et al. An evaluation of endoscopic indication and findings related to nonvariceal upper-GI hemorrhage in a large multicenter consortium. Gastrointest Endosc 2008;67:422-9; and Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107:345-60.

            (b) Variceal UGIB: If active variceal hemorrhage is confirmed, endoscopic and pharmacologic therapy should be initiated.
    b. Therapeutic endoscopy
        i. Can be used in conjunction with a diagnostic endoscopy to treat the source of UGIB once it has been identified
        ii. Non-variceal UGIB
            (a) Peptic ulcer
                (1) Endoscopic therapy should be used for lesions with active spurting, active oozing, or a non-bleeding visible vessel.

            (2) Endoscopic therapy for an adherent clot resistant to vigorous irrigation is controversial. Patients with clinical features associated with a higher risk of rebleeding (e.g., older age) may benefit from endoscopic therapy.
            (3) Endoscopic therapy should not be used for ulcers with a flat pigmented spot or clean base.
            (4) Endoscopic therapy includes hemostatic clips, epinephrine injection, and thermal therapy. Often, these therapies are combined. Epinephrine injection should not be used alone but should be combined with a second modality.
        (b) Other findings (e.g., erosions or Mallory-Weiss tear) are typically unamenable to endoscopic therapy.
    iii. Variceal UGIB
        (a) The primary endoscopic therapy for esophageal varices is endoscopic band ligation, which is preferred to sclerotherapy.
        (b) Sclerotherapy is recommended in patients for whom endoscopic band ligation is unfeasible.
        (c) Gastric varices are often unamenable to endoscopic band ligation, and rescue therapies may be necessary (discussed later in the chapter).

5. Pharmacologic management
    a. Non-variceal UGIB
        i. Acid-suppressive therapy is the mainstay of pharmacologic therapy for acute non-variceal UGIB.
        ii. Gastric acid inhibits platelet aggregation, impairs clot formation, and promotes fibrinolysis. In in vitro studies, inhibiting gastric acid and raising the intragastric pH to 6 or higher may promote clot formation and decrease the risk of rebleeding. However, clinically, a pH of 4–5 should likely be sufficient.
        iii. Histamine-2 receptor antagonists are ineffective at achieving a pH greater than 6 and have shown inconsistent benefit; therefore, these agents are not recommended for patients with acute ulcer-related UGIB.
        iv. Adding octreotide to PPI therapy does not appear to reduce hospital or ICU length of stay, rebleeding, or mortality in patients with nonvariceal UGIB and is not routinely recommended.
        v. High-dose PPIs should be used as an adjunct to endoscopic therapy.
            (a) The most recent American College of Gastroenterology guidelines do not recommend for or against the use of pre-endoscopic PPIs in patients with UGIB. This is a change from prior versions, which stated that pre-endoscopic PPIs could be considered to decrease the need for endoscopic therapy.
            (b) High-dose PPI is defined as 80 mg/day or more for 3 days or more. This can be administered as a continuous infusion or as intermittent boluses.
            (c) High-risk patients with UGIB because of ulcers who underwent endoscopic therapy should receive high-dose PPI treatment for 3 days, followed by twice-daily therapy for 2 weeks after the index endoscopy.
    b. Variceal UGIB
        i. Octreotide, a somatostatin analog, should be initiated promptly when variceal UGIB is suspected and continued for 2–5 days after the diagnosis is confirmed.
            (a) Octreotide causes selective splanchnic vasoconstriction through inhibition of the release of vasodilatory peptides (mainly glucagon). Octreotide may also have a local vasoconstrictive effect. Splanchnic vasoconstriction decreases portal inflow, which indirectly reduces variceal blood flow and hemorrhage volume.
            (b) Typically given as a 50-mcg bolus, followed by a 50-mcg/hour continuous intravenous infusion

    - (c) When used without therapeutic endoscopy, octreotide is only marginally beneficial (i.e., reduction of packed red blood transfusion by 0.7 unit with no benefit on rebleeding or mortality).
    - (d) Compared with endoscopic therapy alone, a somatostatin analog combined with endoscopic therapy is associated with improved initial control of bleeding (relative risk [RR] 1.12; 95% CI, 1.02–1.23) and hemostasis at 5 days (RR 1.28; 95% CI, 1.18–1.39) with no difference in mortality or serious adverse events.
    - (e) Patients should be monitored for bradycardia and hyperglycemia during octreotide infusion.
    - (f) For patients in whom a TIPS is performed successfully, octreotide can be discontinued.
  - ii. Vasopressin infusion is not recommended for variceal UGIB because of the high incidence of adverse events (cardiac, peripheral, and bowel ischemia) with doses necessary to reduce splanchnic blood flow (0.2–0.8 unit/minute).
  - iii. Because of the high incidence of peptic ulcer–related UGIB, high-dose PPI should be initiated, even when variceal UGIB is suspected, until the diagnosis of variceal UGIB is confirmed.
    - (a) There is no evidence that high-dose PPI therapy reduces the risk of rebleeding after endoscopic therapy for variceal UGIB.
  - iv. Patients with cirrhosis, with or without ascites, and UGIB (whether variceal or non-variceal) should be initiated on short-term prophylactic antibiotics.
    - (a) Antibiotics are associated with a lower risk of infection, lower risk of rebleeding, shorter length of stay, and higher survival rates.
    - (b) Guidelines recommend therapy with ceftriaxone 1 g daily. Ceftriaxone is preferred to fluoroquinolones because of the high prevalence of fluoroquinolone resistance. Ceftriaxone should be considered for discontinuation when hemorrhage has resolved and octreotide is discontinued.
    - (c) Prophylactic antibiotic therapy should be continued for no more than 7 days.
  - v. For patients in whom a TIPS is not performed, a nonselective β-blocker (propranolol, nadolol, or carvedilol) should be initiated once octreotide is discontinued unless the patient's heart rate or blood pressure prohibit β-blocker therapy.
  - vi. Simvastatin may be added to standard therapy in patients with cirrhosis and variceal bleeding.
    - (a) A randomized placebo-controlled trial showed that simvastatin did not reduce the rate of rebleeding but was associated with decreased mortality in patients with Child-Pugh class A and B cirrhosis.
    - (b) Patients should be monitored closely for clinical signs and symptoms of rhabdomyolysis.
- c. Treatment of *H. pylori* infection is beyond the scope of this chapter; however, a 14-day treatment should be given to all patients with suspected or diagnosed infection, and eradication should be confirmed 4 weeks after therapy.

6. Rescue therapies
   - a. For patients in whom endoscopic therapy has failed or who are not candidates for endoscopy, angiographic intervention (typically selective arterial embolization) may be required.
   - b. For variceal UGIB, balloon tamponade may be used as a temporizing method (maximum 24 hours) while definitive therapy is planned.
   - c. TIPS is indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs, despite pharmacologic and endoscopic therapy. Patients with Child-Turcotte-Pugh class C cirrhosis or Child-Turcotte-Pugh class B with bleeding on endoscopy may be considered for TIPS within 72 hours.

Patient Case

7. A 27-year-old man with a medical history of Crohn disease presents to your ED with frank bloody output from his rectum. The patient has hypotension (systolic blood pressure 85 mm Hg, MAP 58 mm Hg), and an NG lavage reveals “coffee-ground” material. The resident on call is in the process of calling the endoscopy team to help diagnose and intervene on an UGIB with an esophagogastroduodenoscopy. Which statement is most accurate regarding the care of this patient?

   A. An endoscopy is the appropriate course of action but should not be performed until after initiation of PPI continuous infusion.
   B. A PPI continuous infusion should be initiated as soon as possible and continued for 48 hours post-endoscopy.
   C. The patient, who likely has a lower GI bleed, would benefit from a colonoscopy as opposed to an esophagogastroduodenoscopy.
   D. An endoscopy and a PPI continuous infusion should be initiated as soon as possible.

E. Management of Anticoagulation and Antiplatelet Therapy
   1. Anticoagulation
      a. Patients who do not have a strong indication for continued anticoagulation at the time of the bleeding event should have antithrombotic therapy discontinued.
      b. American College of Gastroenterology recommends against the use of fresh frozen plasma or vitamin K in patients on warfarin hospitalized with GI bleed. Although this group could not reach a consensus regarding the role of PCC for management of GI bleeding in patients receiving warfarin, guidelines suggest the use of PCC over FFP, particularly when bleeding is life-threatening, INR is significantly elevated, or massive blood transfusion is not feasible.
      c. Reversal of dabigatran with idarucizumab is not routinely recommended but may be considered in patients with a life-threatening GI bleed who have taken dabigatran in the past 24 hours.
      d. Use of andexanet alfa is not recommended for patients taking rivaroxaban or apixaban who are hospitalized with a GI bleed.
      e. Administration of PCC for patients hospitalized with GI bleed who have been taking any direct oral anticoagulant is not routinely recommended. However, use may be considered in patients who have taken any of these agents in the past 24 hours and have a life-threatening bleed.
      f. Most patients who develop UGIB while receiving long-term antithrombotic therapy continue to be at risk of thrombosis; these patients should be resumed on antithrombotic therapy.
         i. In a retrospective cohort study of patients who had a GI hemorrhage during warfarin therapy, those who resumed warfarin within 90 days after the hemorrhagic event had a lower adjusted risk of death (HR 0.31; 95% CI, 0.15–0.62) and thrombosis (HR 0.05; 95% CI, 0.01–0.58), without a significant increase in the risk of recurrent GI hemorrhage (HR 1.32; 95% CI, 0.50–3.57). In this study, warfarin was resumed a median of 4 days (interquartile range 2, 9) after presentation for UGIB. These data suggest that for many patients with warfarin-associated GI hemorrhage, the benefits of resuming warfarin therapy outweigh the risks.
         ii. Antithrombotic therapy should be withheld at minimum until the source of bleeding is found and controlled.
         iii. The patient’s short-term risk of rebleeding should be weighed against the short-term risk of thrombosis when deciding to resume antithrombotic therapy.
         iv. Some experts recommend that warfarin be resumed 4–7 days after presentation for UGIB.
         v. The risks, benefits, and timing of resuming target-specific oral anticoagulants are unclear.

2. Antiplatelet therapy
    a. For patients on aspirin for secondary cardiovascular prevention who present with GI bleed, holding aspirin therapy is not recommended. If aspirin is interrupted, it should be resumed within 24 hours of achieving hemostasis.
    b. Timing of reinitiation of other antiplatelet therapy depends on the risk of rebleed determined during endoscopy. If this risk is considered low, P2Y12 receptor blockers may be restarted within 1–3 days after hemostasis. Reinitiation of these agents is further delayed in high-risk patients until the risk has decreased.

VII. ENDOCRINE EMERGENCIES

A. Epidemiology
1. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most common diabetic emergencies.
    a. DKA accounts for 500,000 hospital days and costs up to $5 billion per year in the United States.
    b. Between 2009 and 2014, there was a 54% increase in hospitalization rates for DKA in the United States, with the highest rates in patients younger than 44.
    c. Most patients who develop DKA have type 1 diabetes, and DKA is considered the most important contributor to mortality rates in children and adolescents with diabetes.
    d. In-hospital mortality rates for DKA are 0.2%–1.4%, and can be as high as 5%–20% for HHS, depending on age and other comorbidities.
2. Hyperglycemia (BG above 140 mg/dL) occurs commonly in the setting of critical illness, with prevalence rates depending on the level of hyperglycemia and patient population evaluated.
    a. About 27% of critically ill patients have a BG above 200 mg/dL on ICU admission, and about 90% of patients will have at least one BG reading above 110 mg/dL during their ICU stay.
    b. Hyperglycemia has consistently been associated with increased mortality in critically ill patients, most notably in patients without diabetes. The link between hyperglycemia and worse outcomes seems strongest for patients with acute coronary syndrome or stroke.
    c. Glucose variability (BG fluctuation over time) has also been associated with ICU mortality.
3. Hypoglycemia also occurs commonly in the ICU, both with and without intensive glucose control.
    a. In a large international cohort of patients, moderate hypoglycemia (BG less than 70 mg/dL) occurred in 37% of patients and was independently associated with mortality on multivariable regression (OR 1.78; 95% CI, 1.39–2.27).
    b. In a secondary analysis of the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, moderate hypoglycemia occurred in 45% of patients (74.2% in the intensive-control group and 15.8% in the conventional-control group), and severe hypoglycemia (BG below 40 mg/dL) occurred in 3.7% of patients (6.9% in the intensive-control group and 0.5% in the conventional-control group). Both moderate and severe hypoglycemia (HR 1.41; 95% CI, 1.21–1.62 and HR 2.10; 95% CI, 1.59–2.77, respectively) were independently associated with death compared with the absence of hypoglycemia.
4. Thyroid crisis, also known as thyroid storm or critical thyrotoxicosis, is an uncommon manifestation of hyperthyroidism known to occur in less than 10% of patients admitted for thyrotoxicosis. Thyrotoxicosis has been associated with mortality rates of 8%–25%, if treated, and up to 100%, if untreated.
5. Myxedema coma is an uncommon severe manifestation of hypothyroidism, with mortality rates of about 20%–25% with appropriate treatment and up to 80% without treatment.

6. Adrenal crisis (i.e., acute adrenal insufficiency or Addisonian crisis) is a life-threatening disorder caused by glucocorticoid (and possibly mineralocorticoid) deficiency.
    a. Adrenal crisis necessitating hospital admission has an incidence of 3.3 per 100 patient-years in those with chronic adrenal insufficiency.
    b. Critical illness–related corticosteroid insufficiency (CIRCI) is a separate entity from adrenal crisis. The prevalence of CIRCI is about 10%–20% but depends on the definition used and the population evaluated. Prevalence rates as high as 60% for patients with septic shock have been reported.

B. DKA and HHS
1. Clinical presentation of DKA
    a. Current guidelines define DKA as a combination of hyperglycemia (BG greater than 200 mg/dL or prior history of diabetes), ketosis (positive urine or serum ketones), and acidosis (pH less than 7.30 and/or bicarbonate concentration less than 18 mmol/L). Patients with severe DKA present with severe acidemia (pH less than 7), a serum bicarbonate less than 10 mmol/L, and depressed mental status (stupor or coma).
        i. Guidelines were updated with a new definition of hyperglycemia in 2024 to reflect the increasing percentage of patients who present with euglycemic DKA.
    b. Serum glucose concentrations are usually less than 800 mg/dL but may be more elevated in patients who are comatose. In the setting of starvation, pregnancy, treatment with insulin prior to presentation, or use of sodium-glucose- cotransporter 2 inhibitors, glucose may be normal or only mildly elevated.
    c. A lack of insulin leads to reduced glucose uptake, which, together with increased counterregulatory hormone (catecholamines, cortisol, glucagon, and growth hormone) release, leads to increased lipolysis. The released free fatty acids are metabolized in the liver to ketone bodies (β-hydroxybutyrate and acetoacetate), resulting in ketonemia and elevated anion gap metabolic acidosis.
    d. Although symptoms may exist for a few days, ketoacidosis occurs quickly, and patients may deteriorate rapidly.
    e. Typically occurs in young, leaner patients with type 1 diabetes
    f. Patients may present with symptoms of nausea and vomiting (80% of patients; more indicative of DKA than of HHS), polyuria, polydipsia, weight loss, abdominal pain (30% of patients), and fruity breath from acetone in the blood. Signs of DKA include tachycardia, poor skin turgor, hypotension (because of intravascular volume loss from osmotic diuresis), and Kussmaul respirations (due to severe acidemia).
    g. Measured serum potassium may be high because hyperosmolality, and lack of endogenous insulin causes intracellular potassium ions to shift into the extracellular space. However, patients typically have a relative deficiency of total body potassium, which can be worsened with insulin treatment.
2. Clinical presentation of HHS
    a. HHS is defined as BG greater than 600 mg/dL and elevated serum osmolarity (calculated effective serum osmolality greater than 300 mOsm/kg or total serum osmolality greater than 320 mOsm/kg) with pH greater than 7.3 and serum bicarbonate greater than or equal to 15 mmol/L. Ketones are not present or only measured in small amounts.
    b. HHS presentation is often later in the disease course than DKA (because of the lack of ketosis), and symptoms evolve over days to weeks. Patients also have higher degrees of dehydration owing to osmotic diuresis.
    c. More common in older patients with obesity with type 2 diabetes
    d. Signs and symptoms, including electrolyte abnormalities, are similar to those in DKA. However, confusion is much more apparent in HHS and is directly related to the serum osmolality.

   e. Patients with HHS do not normally develop ketoacidosis. Although there is an overall insulin deficiency in both DKA and HHS, there is enough insulin secretion to prevent ketogenesis in patients with HHS.
   f. Lack of access to water, either because of the illness itself or because of an altered thirst response in older adult patients, can worsen the severity of dehydration in the setting of hyperglycemia.
3. Typically, DKA and HHS are caused by an insufficiency of insulin in patients with diabetes combined with another potential trigger such as infection, medication nonadherence, myocardial infarction, cerebrovascular accident, pancreatitis, and certain drugs (i.e., steroids, diuretics, vasopressors, antipsychotics, cocaine, sodium-glucose cotransporter 2 inhibitors).
4. Management
   a. Primarily involves fluid resuscitation, correction of hyperglycemia, and electrolyte (mainly potassium) replacement. Correction of acidemia may also be indicated.
   b. Patients are often profoundly hypovolemic. Total body water deficits may be as high as 10–12 L and should be replaced within the first 24 hours.
      i. In the absence of concomitant cardiogenic shock, 0.9% sodium chloride should be administered at a rate of 15–20 mL/kg (typically 1–1.5 L) for the first hour. Thereafter, fluid administration is titrated to hemodynamic parameters and urine output (i.e., fluid infusion rates typically 250–500 mL/hour).
      ii. Patients with mild dehydration and normal or high sodium concentrations can be changed to 0.45% sodium chloride infused at a rate of 250–500 mL/hour.
      iii. Maintenance fluids can be switched to a dextrose-containing fluid (often 5% dextrose with 0.45% sodium chloride) once BG concentrations have dropped to less than 200 mg/dL in DKA and less than 300 mg/dL in HHS.
      iv. Serum sodium concentration should be considered when choosing resuscitation fluid because rapid correction of hypernatremia may have severe consequences.
      v. Recent studies suggest that time to DKA resolution may be shorter when balanced crystalloids are used for resuscitation in place of saline, but further studies are needed to confirm benefit.
   c. Insulin therapy is the main treatment modality of DKA and HHS.
      i. Insulin corrects hyperglycemia and inhibits the release of free fatty acids, which decreases ketone formation and corrects acidosis.
      ii. Intravenous regular insulin is preferred to subcutaneous insulin because of its short half-life and ease of titration.
      iii. Initiate with a 0.1-unit/kg intravenous bolus, followed by a 0.1-unit/kg/hour continuous infusion. Bolus dosing may vary by patient and institution; if bolus is given, BG should be monitored closely to avoid hypoglycemia. An alternative approach, without an initial bolus but initiated at a higher continuous infusion rate (0.14 unit/kg/hour), provides a time similar to DKA resolution.
      iv. The insulin infusion should subsequently be titrated on an hourly basis to decrease BG concentrations by 50–75 mg/dL/hour.
      v. DKA: Decrease dose to 0.02–0.05 unit/kg/hour once BG concentrations drop to 200 mg/dL, and maintain a BG of 150–200 mg/dL until ketoacidosis has resolved.
      vi. HHS: Decrease dose to 0.02–0.05 unit/kg/hour once BG concentrations drop to 300 mg/dL, and maintain a BG of 200–300 mg/dL until mental status changes have resolved.

vii. Continuous insulin infusions should be continued until ketoacidosis resolves in DKA and abnormal serum osmolality and mental status in HHS resolve; then, change to subcutaneous insulin.
   (a) Criteria for resolution of ketoacidosis include a BG less than 200 mg/dL and two of the following: a serum bicarbonate concentration of 15 mEq/L or greater, a venous pH greater than 7.3, and a normalization of anion gap. Per guidelines, anion gap should be 12 mEq/L or less, but normal range may vary by institution.
   (b) For patients with new insulin requirement, doses of 0.5–0.8 units/kg of subcutaneous insulin per day can be used with a basal (glargine or detemir) and bolus (lispro, aspart, or glulisine). For patients previously on subcutaneous insulin therapy, outpatient insulin requirement can be used to guide dosing; weight-based dosing may be insufficient for those who have high baseline requirements. There should be an overlap of 1–2 hours between administration of subcutaneous insulin and discontinuation of intravenous insulin infusion.
   (c) Subcutaneous insulin can be used in patients with mild or moderate DKA or HHS but have not been evaluated in patients with severe disease.
      (1) Basal insulin is started at a dose of 0.15–0.3 units/kg and repeated every 12–24 hours.
      (2) An initial bolus of 0.2 units/kg of rapid acting insulin is also given. Subsequent doses of rapid acting insulin are repeated every 2–4 hours until DKA has resolved.

d. Potassium should be replaced aggressively (assuming adequate renal function) with a goal serum potassium of 4–5 mEq/L.
   i. Patients with initial serum potassium less than 3.3 mEq/L should have insulin withheld and potassium administered until their serum potassium is above 3.3 mEq/L.
   ii. Patients with serum potassium of 3.3–5.2 mEq/L should have 20–30 mEq of potassium added to each liter of intravenous fluid administered.
   iii. Patients with initial serum potassium greater than 5.2 mEq/L should not receive potassium, but they should be monitored closely (with potassium administered if the patient's serum falls below 5 mEq/L). Of importance, patients with DKA and initial hyperkalemia should not receive therapy directed toward total body potassium removal (e.g., sodium polystyrene sulfonate or furosemide). The patient's serum potassium will typically decrease as insulin is administered.

e. Intravenous sodium bicarbonate should not be administered routinely.
   i. Acidemia will typically quickly correct as ketosis is resolved, and bicarbonate may have deleterious effects (e.g., hypokalemia).
   ii. Studies of patients with DKA with a pH of 6.9 or greater have not supported a benefit with sodium bicarbonate administration.
   iii. A recent study of sodium bicarbonate in ICU patients showed a potential mortality benefit in patients with acute kidney injury. However, this study excluded patients with ketoacidosis.
   iv. Guidelines recommend administering bicarbonate in the setting of severe metabolic acidosis (pH less than 7).
      (a) Suggested dosing regimen is 100 mL of 8.4% sodium bicarbonate solution in 400 mL of sterile water every 2 hours to achieve pH greater than 7. Phosphorus repletion should be initiated in patients with serum phosphate below 1 mg/dL or in those with severe cardiac or respiratory dysfunction associated with hypophosphatemia.

C. Hyperglycemia
   1. Clinical presentation
      a. Because hyperglycemia is so prevalent in critically ill patients, there is no specific clinical presentation.

b. Critically ill patients often do not have the “classic triad” of diabetes symptoms of polyuria, polydipsia, and polyphagia.
c. Stress-induced hyperglycemia has been associated with illness severity.

2. Causes
   a. Critically ill patients have increased release of “stress hormones” (e.g., cortisol and epinephrine) and cytokines. These responses lead to both increased glucose production and insulin resistance, which results in hyperglycemia.
   b. Hyperglycemia is further exacerbated by infusions of dextrose-containing fluids, corticosteroids, and exogenous sympathomimetic medication administration.
3. Management
   a. Hyperglycemia was once considered a beneficial adaptive response in the critically ill population and was not considered a treatment priority. In general, BG was only treated if it exceeded 200 mg/dL.
   b. Tighter glucose control garnered increased interest because hyperglycemia has independently been associated with increased ICU mortality.
   c. A treatment paradigm shift occurred in 2001 with the publication of the landmark “intensive insulin therapy” study.
      i. In this single-center study, surgical ICU patients who were receiving parenteral nutrition were randomized to intensive intravenous insulin therapy (goal BG 80–110 mg/dL) or conventional insulin therapy (goal BG 180–200 mg/dL).
      ii. Patients randomized to intensive insulin therapy had a significantly lower ICU mortality rate than patients receiving conventional insulin therapy (4.6% vs. 8.0%, $p<0.04$). The ICU mortality benefit was most pronounced in patients who stayed in the ICU (and received intensive insulin therapy) for greater than 5 days (10.6% vs. 20.2%, $p=0.005$).
      iii. Patients randomized to intensive insulin therapy also less commonly developed bloodstream infections, acute kidney injury, and ICU-acquired weakness (at the time termed *critical-illness polyneuropathy*).
      iv. A study of medical ICU patients with an identical design from the same center was published in 2006. The study detected no in-hospital mortality benefit with intensive insulin therapy (37.3% vs. 40.0% with conventional insulin therapy, $p=0.33$). Patients in the intensive insulin therapy arm less commonly developed acute kidney injury, had a shorter time to liberation from mechanical ventilation, and had earlier discharge from the ICU and hospital. For patients who stayed in the ICU for 3 days or more, in-hospital mortality was lower in the intensive insulin therapy arm (43.0% vs. 52.5%, $p=0.009$), but the validity of this subgroup analysis has been called into question because patients were not defined by a baseline characteristic.
      v. In light of these findings, intensive insulin therapy was widely recommended by treatment guidelines (including the 2008 Surviving Sepsis Campaign guidelines) and often implemented into practice as a standard of care.
   d. Multicenter trials do not support routine use of intensive insulin therapy.
      i. Because of concern with the single-center nature of the aforementioned studies, unblinded design, and large relative mortality benefit, three multicenter trials were designed and conducted.
      ii. One multicenter study was terminated early because of safety concerns. Patients randomized to intensive insulin therapy more commonly developed severe hypoglycemia (BG of 40 mg/dL or less) than those allocated to conventional insulin therapy (17.0% vs. 4.1%, $p<0.001$). Intensive insulin therapy was not associated with a benefit in 28-day mortality (24.7% vs. 26.0%, $p=0.74$), but the study was inadequately powered to assess this outcome.

iii. A second multicenter study was terminated early because of several protocol violations. Intensive insulin therapy was not associated with a benefit in ICU mortality (17.2% vs. 15.3%, p=0.41), but patients allocated to intensive insulin therapy more commonly developed severe hypoglycemia (BG of 40 mg/dL or less; 8.7% vs. 2.7%, p<0.0001).

iv. The NICE-SUGAR study, evaluated intensive insulin therapy (target BG 81–108 mg/dL) or conventional glucose control (BG of 180 mg/dL or less) in more than 3000 patients.
   (a) At 90 days, intensive insulin therapy was associated with increased mortality (27.5% vs. 24.9%, p=0.02).
   (b) Severe hypoglycemia (BG of 40 mg/dL or less) was more common in patients allocated to intensive insulin therapy (6.8% vs. 0.5%, p<0.0001).
   (c) Intensive insulin therapy was not associated with a benefit in ICU or hospital length of stay, days of mechanical ventilation, or need for renal replacement therapy.

v. A 2023 randomized study of 9230 medical and surgical ICU patients compared liberal glucose control (insulin initiated when BG greater than 215 mg/dL) to intensive insulin control (BG goal 80–110 mg/dL).
   (a) Median absolute difference in daily BG between groups was about 28 mg/dL.
   (b) There were no differences between groups for ICU length of stay, 90-day mortality, or severe hypoglycemia between groups.

e. A meta-analysis that included seven randomized controlled trials and 11,425 patients found that intensive insulin therapy was not associated with a difference in 28-day mortality (OR 1.04; 95% CI, 0.93–1.17) but was associated with a significant increase in the incidence of hypoglycemia (OR 7.7; 95% CI, 6.0–9.9).

f. The 2024 Society of Critical Care Medicine Guidelines on Glycemic Control for Critically Ill Children and Adults consider it good practice to maintain blood glucose less than 180 mg/dL through evaluation of glucose intake, additional monitoring, and insulin therapy.
   i. Guidelines suggest against titrating insulin infusion to goal BG of 80–139 mg/dL and favor a target of 140–200 mg/dL to reduce risk of hypoglycemia.

D. Hypoglycemia

1. Clinical presentation
   a. Glucose is an obligate molecule for brain function. The brain cannot produce glucose, efficiently use alternative fuels, or store substantial amounts of glycogen, so maintenance of brain function requires a continuous supply of glucose from the circulation.
   b. Multiple mechanisms exist to maintain blood glucose within physiologic range. These complex pathways are multifaceted and include pancreatic (decreased insulin and increased glucagon), central nervous system (CNS) (increased norepinephrine and acetylcholine), adrenal medulla (increased epinephrine), and liver (increased glycogenolysis and gluconeogenesis) involvement.
   c. In the early stages of hypoglycemia, symptoms such as sweating, anxiety, hunger, palpitations, tremor, and arousal are present. As hypoglycemia persists and worsens, confusion, dizziness, and difficulty speaking develop. Severe hypoglycemia leads to seizures and hypoglycemic coma.
   d. Typically, complete recovery of symptoms occurs with glucose administration, but permanent brain damage may occur in patients with severe prolonged hypoglycemia.
   e. Hypoglycemia, a reversible cause of cardiac arrest, should be considered for patients with an unclear reason for cardiac arrest.
   f. Neurologic symptoms of hypoglycemia may be masked by sedation, and the counterregulatory response may be impaired or masked (e.g., in circulatory shock).

2. Causes
   a. Hypoglycemia can be caused by excessive insulin administration, reduced intake of glucose (rarely the cause of severe hypoglycemia in the absence of insulin administration), decreased insulin resistance (weight loss, adrenal or pituitary insufficiency), decreased clearance of insulin (renal or hepatic insufficiency), or other drugs (commonly sulfonylureas, meglitinides, and ethanol; possibly pentamidine, quinine, quinolones, insulin-like growth factor 1, β-blockers, or ACE inhibitors).
   b. In a retrospective cohort study of mixed ICU patients, independent predictors of hypoglycemia (BG less than 45 mg/dL) included continuous venovenous hemofiltration with bicarbonate-based replacement solution (OR 14; 95% CI, 1.8–106), a decrease of nutrition without adjustment for insulin infusion (OR 6.6; 95% CI, 1.9–23), diabetes (OR 2.6; 95% CI, 1.5–4.7), insulin use (OR 5.3; 95% CI, 2.8–11), sepsis (OR 2.2; 95% CI, 1.2–4.1), and inotropic support (OR 1.8; 95% CI, 1.1–2.9).
   c. Other studies of critically ill patients have identified renal insufficiency, diabetes, mechanical ventilation, female sex, greater severity of illness, longer ICU stay, liver disease, immunocompromised state, and medical or nonelective admission as risk factors for hypoglycemia.
   d. Renal insufficiency in the setting of insulin administration should be particularly noted because patients with renal failure have decreased clearance of insulin, which may prolong the duration of hypoglycemia.
3. Management
   a. For conscious patients without severe symptoms, oral glucose should be ingested (juice, soda, or dextrose tablets).
      i. The typical initial glucose dose is 15 g, which should be repeated in 15–20 minutes if symptoms have not improved or if BG remains low.
      ii. Because the response to this "rescue glucose" is transient (less than 2 hours), it should be followed by more substantial glucose intake as a snack or meal.
   b. Parenteral therapy is necessary for patients unable to take glucose orally or hospitalized patients with moderate or severe hypoglycemia.
      i. Glucagon 1 mg promotes hepatic glucogenesis and glycogenolysis. It is a useful therapy for patients with type 1 diabetes (often outside a health care setting) and those without diabetes, but it is less useful in patients with type 2 diabetes because it stimulates insulin secretion and glycogenolysis. Nausea/vomiting is a common adverse effect of glucagon.
      ii. Hospitalized patients with severe hypoglycemia (either severe symptoms or BG less than 40 mg/dL) or those receiving an insulin infusion with BG less than 70 mg/dL (less than 100 mg/dL in neurologic injured patients) should be treated with intravenous dextrose.
         (a) Insulin infusion should be discontinued, as appropriate.
         (b) Administer 10–20 g of 50% dextrose solution (20–40 mL of 50% dextrose in water).
         (c) The BG measurement should be repeated in 15 minutes, with additional dextrose doses administered to achieve a BG greater than 70 mg/dL.
         (d) Care should be taken to avoid excessive dextrose administration in order to avoid iatrogenic hyperglycemia and because glucose variability has been associated with adverse outcomes.
         (e) To prevent hypoglycemia, the insulin regimen should be reassessed if BG is less than 100 mg/dL.

E. Thyroid Crisis
1. Clinical presentation
   a. Thyroid crisis is characterized by severe manifestations of hyperthyroidism.
   b. Diagnosis can be established on the basis of clinical presentation in a patient with laboratory evidence of hyperthyroidism.

i. Hyperthermia and diaphoresis are cardinal manifestations of thyroid crisis. Other key components include tachycardia out of proportion to fever and gastrointestinal dysfunction (nausea, vomiting, diarrhea, jaundice).
ii. In progressive thyroid crisis, patients may develop mental status changes (e.g., agitation, psychosis, coma), and altered mentation has been associated with higher mortality. Other clinical manifestations include cardiac arrhythmias, heart failure, and tachypnea.
iii. Serum TSH is often below the normal range with elevated free T_3 and free and total T_4. Total T_3 levels may be within normal limits in patients with a precipitating illness that reduces T_4 to T_3 conversion.
iv. Other laboratory abnormalities include hypercalcemia, hyperglycemia, leukocytosis or leukopenia, and elevated liver function tests.
v. No universally accepted diagnostic criteria exist, but the Burch and Wartofsky criteria (Table 7) can be used to identify potential thyroid storm. Although this scoring system is effective, it is not highly specific.

Table 7. Burch and Wartofsky Criteria for Thyroid Storm

Criteria	Points
Temperature (°F)	
• 99–99.9	5
• 100–100.9	10
• 101–101.9	15
• 102–102.9	20
• 103–103.9	25
• ≥ 104	30
Heart rate (beats/minute)	
• 99–109	5
• 110–119	10
• 120–129	15
• 130–139	20
• ≥ 140	25
Atrial fibrillation	
• Absent	0
• Present	10
Congestive heart failure	
• Absent	0
• Mild (edema)	5
• Moderate (rales)	10
• Severe (pulmonary edema)	20
GI signs	
• Absent	0
• Moderate (nausea, vomiting, diarrhea, abdominal pain)	10
• Severe (jaundice)	20
CNS disturbance	
• Absent	0
• Mild (agitation)	10
• Moderate (delirium, psychosis, extreme lethargy)	20
• Severe (seizure, coma)	30

Table 7. Burch and Wartofsky Criteria for Thyroid Storm *(continued)*

Criteria	Points
Precipitant history • Positive • Negative	 0 10
Score • > 44: Thyroid storm • 25–44: Suggestive/impending storm • < 25: Storm unlikely	

Information from: Bahn RS, Burch HB, Cooper DS, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011;21:593-646.

2. Causes
    a. Thyroid crisis can develop in patients with a history of untreated hyperthyroidism but is more often precipitated by an acute event. Precipitating events include surgery, pregnancy, and trauma. In hospitalized patients, the most common cause is infection.
    b. Drugs associated with thyroid crisis include radioactive iodine, overdose of levothyroxine or liothyronine, cytotoxic chemotherapy, aspirin, iodinated contrast dye, amiodarone, and organophosphate toxicity.
    c. Rarely, thyroid crisis is the initial presentation for patients with undiagnosed hyperthyroidism.
3. Management
    a. Treatment of thyroid crisis is complex and requires several interventions simultaneously.
    b. Decrease thyroid hormone synthesis.
        i. Methimazole and propylthiouracil inhibit production of new thyroid hormone.
        ii. Propylthiouracil is preferred in thyroid crisis because it not only blocks new thyroid synthesis but also decreases peripheral conversion of T_4 to T_3.
        iii. Propylthiouracil is also preferred in the first trimester of pregnancy; after the start of the second trimester, patients may continue propylthiouracil or transition to methimazole. Concentrations of both agents in breast milk are low, but methimazole is generally preferred in breastfeeding mothers due to risk of hepatotoxicity with propylthiouracil.
        iv. Propylthiouracil is given as a 500- to 1000-mg loading dose, followed by 250 mg every 6 hours. Doses may be given enterally or rectally.
        v. Patients receiving propylthiouracil should be monitored for adverse effects, including agranulocytosis, allergic hepatitis, and vasculitis.
        vi. If methimazole is used because of propylthiouracil allergy or intolerance, usual dose is 20–30 mg every 8 hours. Doses may be given enterally or rectally.
        vii. Intravenous steroids (hydrocortisone 300-mg loading dose, followed by 100 mg every 8 hours) should be initiated to block the conversion of T_4 to T_3.
        viii. Plasmapheresis has been used to remove cytokines, antibodies, and thyroid hormones from plasma when traditional therapies have not been successful. Effects are transient, lasting 24–48 hours, but improvement in clinical status has enabled patients to be stabilized for definitive therapy with thyroidectomy.
    c. Inhibit thyroid hormone release with inorganic iodine.
        i. Propylthiouracil and methimazole inhibit thyroid hormone synthesis but do not block release of stored hormone from the thyroid gland.
        ii. Initial dose of iodine should be given at least 1 hour after the first dose of propylthiouracil or methimazole to reduce the risk of providing more substrate for thyroid hormone production.
        iii. Oral potassium iodide (Lugol solution) is administered as 3–5 drops every 6 hours. If available, sodium iodide can be given as an intravenous infusion of 0.5–1 g over 24 hours.

- iv. In patients who are allergic to iodine, lithium carbonate may be used as an alternative. Initial dose should be 300 mg every 6 hours, with subsequent adjustment to maintain serum lithium concentration of 0.8–1.2 mEq/L.

- d. Reduce levels of circulating thyroid hormone.
  - i. Cholestyramine can be given to bind circulating T_3 and T_4.
  - ii. Salicylates should be avoided because use can decrease binding of thyroid hormones to proteins and therefore increase concentrations of free thyroid hormones.
  - iii. In severe cases that do not respond to standard therapy, plasmapheresis and therapeutic plasma exchange may be considered to decrease T_4 and T_3 levels.
- e. Reduce heart rate.
  - i. Because cardiovascular collapse leads to systemic decompensation, β-blockers should be initiated as quickly as possible.
  - ii. β-Blocker dose should be titrated to achieve heart rate control (typically below 90 beats/minute).
  - iii. Traditionally, propranolol is the preferred therapy because it may block T_4 to T_3 conversion at high doses. Propranolol is also the agent of choice in women who are pregnant or breastfeeding. Dosing for this indication is aggressive, starting at 60 mg orally every 4 hours with an optional initial loading dose of 80 mg.
  - iv. Alternative agents include carvedilol, esmolol, and diltiazem. Diltiazem should be reserved for patients with active bronchospasm or for those who do not tolerate β-blockers.

F. Myxedema Coma

- 1. Clinical presentation
  - a. Myxedema coma is defined as decompensated hypothyroidism that leads to multiorgan failure. Despite its name, the primary manifestation of the disease is decline in mental status rather than edema or coma.
  - b. Diagnosis is made on the basis of clinical presentation, not laboratory evidence of hypothyroidism.
    - i. Altered mental status and hypothermia are the most common presenting symptoms. Other clinical features include hypotension, bradycardia, hypoglycemia, constipation, urinary retention, puffiness of the hands and face, and pleural, pericardial, or peritoneal effusions.
    - ii. Patients may present with shock or arrhythmias, including prolongation of the QT interval that can lead to torsades de pointes.
    - iii. If a patient presents with signs of infection without the systemic inflammatory response syndrome, myxedema coma should be suspected.
    - iv. Patients typically have elevated TSH and low or undetectable T_3 and T_4, but TSH may be inappropriately low or normal in cases of central hypothyroidism. The level of change in thyroid hormones does not correlate well with disease severity.
  - c. Myxedema coma is more common in older women and occurs more often during winter months because of altered temperature regulation.
  - d. Discussion of nonthyroidal illness syndrome (“euthyroid sick syndrome” or “SICU thyroid”) is beyond the scope of this chapter.
- 2. Causes
  - a. Myxedema coma may be the consequence of longstanding hypothyroidism but can also be precipitated by an acute event such as infection, myocardial infarction, surgery, or cold exposure.
  - b. Drugs associated with the development of myxedema coma include sedatives, anesthetics, narcotics, lithium, immune checkpoint inhibitors, and amiodarone, as well as abrupt discontinuation of levothyroxine.
- 3. Management
  - a. Because myxedema coma is an endocrine emergency, treatment should be initiated without waiting for laboratory data.

b. General treatment measures include rewarming of the patient and treatment of the precipitating illness. Because infection is a common precipitator of myxedema coma, all patients should undergo a thorough infectious workup.

c. Guidelines from the American Thyroid Association recommend the following for patients with myxedema coma:
   i. Patients may have underlying adrenocorticotropic hormone deficiency, and restoration of thyroid function can accelerate cortisol metabolism. Empiric intravenous corticosteroids at doses appropriate for the stressed state should be administered before levothyroxine (strong recommendation). Hydrocortisone is typically given in doses of 50 mg every 6 hours or 100 mg every 8 hours.
   ii. Thyroid hormone replacement should be initiated with intravenous levothyroxine. A loading dose of 200–400 mcg should be given, with lower doses used in patients who are smaller or older or who have a history of cardiac disease or arrhythmia (strong recommendation).
   iii. After the initial loading dose, the daily replacement dose should be 1.6 mcg/kg body weight intravenously (strong recommendation). Daily therapy may be changed to the enteral route after the patient improves clinically.
   iv. Because T_4 to T_3 conversion may be decreased in myxedema coma, intravenous liothyronine may be given in addition to levothyroxine (weak recommendation). High serum T_3 during treatment is associated with mortality, so high doses should be avoided. A loading dose of 5–20 mcg can be given, followed by 2.5–10 mcg every 8 hours. Patients who are smaller or older or who have a history of cardiac disease or arrhythmia should receive smaller doses. Treatment can be continued until the patient has regained consciousness and clinical parameters have improved.
   v. Patients should be monitored for improvements in mental status, cardiac function, and pulmonary function.
   vi. Measurement of thyroid hormones every 1–2 days is reasonable to ensure a favorable trajectory. Optimal levels of TSH, T_4, and T_3 in this scenario have not been defined, but lack of improvement may be an indication to increase the levothyroxine dose and/or add liothyronine. High serum T_3 can be considered an indication to decrease therapy for safety reasons (weak recommendation).

d. Patients may need supportive care with vasoactive medications. Typically, a catecholamine agent with β_1-adrenergic receptor agonist properties (epinephrine or dopamine) is preferred to increase the patient's heart rate and blood pressure.

Patient Case

8. A 23-year-old man (weight 80 kg) presents to the ED with an acute mental status change and a core body temperature of 94°F (34.4°C). He has a history of hypothyroidism, but according to his family, he had decided to stop taking all of his thyroid medications 1 week earlier. The team has given him a diagnosis of myxedema coma. Which is the most appropriate treatment option for this patient?
   A. Intravenous levothyroxine 400 mcg × 1 followed by 125 mcg daily.
   B. An insulin infusion titrated to a BG of 140–180 mg/dL.
   C. Propylthiouracil 200 mg every 4 hours.
   D. Propranolol 60 mg orally every 4 hours.

G. Adrenal insufficiency
  1. Adrenal crisis
    a. Clinical presentation
      i. Because there is no universally accepted evidence-based definition of adrenal crisis, cases are identified based on a pragmatic definition and clinical assessment. In adults, adrenal crisis is defined as an acute deterioration in health status associated with absolute or relative hypotension (SBP less than 100 mm Hg or 20 mm Hg or more below baseline) that improves within 1–2 hours after parenteral glucocorticoid administration. Adrenal crisis is a rare cause of vasodilatory shock.
      ii. Patients with acute adrenal insufficiency typically present with severe hypotension, altered mental status, acute abdominal pain, vomiting, and fever. As such, patients often receive a misdiagnosis of an acute abdomen. Accompanying symptoms may include fatigue, lethargy, confusion, weakness, and pain in the muscles or joints. Patients with primary adrenal insufficiency may also have salt craving (because of mineralocorticoid deficiency secondary to a lack of aldosterone). Characteristic skin hyperpigmentation from primary adrenal insufficiency may also be present.
      iii. Laboratory findings will include low serum cortisol (i.e., cortisol level below 18 mcg/dL in an acutely stressed patient is suggestive of adrenal insufficiency); hyponatremia, hyperkalemia, hypoglycemia, and normocytic anemia may also be present.
    b. Causes
      i. Adrenal crisis may result from primary adrenal failure or secondary adrenal disease.
      ii. Acute-onset primary adrenal insufficiency is most often caused by adrenal hemorrhage or infarction. Common causes of secondary adrenal crisis include pituitary apoplexy, pituitary or hypothalamic surgery, or traumatic brain injury.
      iii. Patients on chronic corticosteroid therapy who experience acute stress (e.g., infection or surgery) will be unable to increase their cortisol appropriately because of suppression of corticotropin-releasing hormone and corticotropin.
      iv. Bacterial infections commonly precipitate adrenal crisis in adults. In children, viral infections are more common precipitating events.
      v. Medications may contribute to inadequate serum cortisol concentrations, including etomidate and ketoconazole. Adrenal crisis has also been reported after vaccinations and zoledronic acid infusions. Case series describe adrenal insufficiency following immune checkpoint inhibitor therapy.
      vi. Abrupt decrease in dose or cessation of corticosteroids in patients receiving moderate to high doses (greater than or equal to prednisone 7.5 mg daily or equivalent) for 3 weeks or more may precipitate adrenal crisis.
    c. Management
      i. Treatment should be initiated as soon as diagnosis is suspected and does not need to be delayed for the results of diagnostic tests.
      ii. Patients with acute adrenal crisis should receive intravenous fluids and vasopressors if shock is present. After initial bolus, dextrose may be added for treatment of hypoglycemia.
      iii. Glucocorticoids should be administered quickly. Hydrocortisone is preferred because of its protein binding, tissue distribution, and balanced glucocorticoid and mineralocorticoid effects; it is typically given as a 100 mg intravenous initial bolus followed by 50 mg intravenously every 6 hours. Alternatives include methylprednisolone 20 mg intravenously twice daily or dexamethasone 4–6 mg intravenously daily. Doses can be tapered based on patient’s clinical status.

    iv. Patients receiving chronic corticosteroids who have an acute stressor should receive an increased glucocorticoid dose to prevent adrenal crisis.
        (a) Recommended dose depends on the level of stress.
        (b) In febrile patients, those undergoing major dental procedures, and those undergoing invasive diagnostic tests (e.g., colonoscopy), a doubling or tripling of the maintenance dose for 1–3 days may be sufficient.
        (c) Patients experiencing severe infection, undergoing major surgery, or presenting with shock should be started on intravenous hydrocortisone 200–300 mg/day, which can be tapered to their home regimen when they have clinically improved.

2. CIRCI
    a. Clinical presentation
        i. CIRCI refers to impairment of the hypothalamic-pituitary-adrenal axis during critical illness as a complication of an underlying disease. Patients most commonly have septic shock but may also have acute respiratory distress syndrome, cardiac arrest, trauma, or burns.
        ii. Patients with CIRCI often have hypotension refractory to fluids that requires addition of vasopressors. Laboratory assessment may show hypoglycemia and eosinophilia; hyponatremia and hyperkalemia are uncommon.
    b. Diagnosis
        i. CIRCI has historically been diagnosed based on either a low serum cortisol concentration or an inadequate response seen on the cosyntropin stimulation test. Poor reproducibility of the cosyntropin stimulation test and lack of agreement of commercially available cortisol assays with analytic standards limit the use of these tests in critically ill patients.
        ii. Despite known limitations, increase in cortisol of less than 9 mg/dL following a cosyntropin stimulation test is the best predictor of adrenal insufficiency. A serum cortisol value less than 10 mg/dL has high positive predictive value for adrenal insufficiency but low sensitivity.
        iii. Current guidelines for the treatment of CIRCI recommend against using cortisol-based testing to determine whether a patient is a candidate for corticosteroid therapy.
    c. Management
        i. Corticosteroids should only be given for patients with septic shock and suspected CIRCI who do not achieve resuscitation goals despite fluid administration and an ongoing vasopressor requirement.
        ii. Treatment of CIRCI in the setting of septic shock is discussed in the “Shock Syndromes I: Introduction, Vasodilatory, and Sepsis” chapter. Use of corticosteroids for the treatment of acute respiratory distress syndrome is discussed in the “Pulmonary Disorders I” chapter.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

Intravenous acetylcysteine increases transplant-free survival rates for patients with NAI-ALF, particularly for patients with low-grade encephalopathy. Oral acetylcysteine has not been studied in a randomized controlled trial for NAI-ALF (Answer C is incorrect), and the dosing strategy for NAI-ALF is different from the 21-hour intravenous regimen for acetaminophen overdose (Answer A is incorrect). The dosing strategy for NAI-ALF is a 72-hour regimen with a 150-mg/kg bolus, followed by a 12.5-mg/kg/hour dose for 4 hours and then a 6.25-mg/kg/hour dose for 67 hours (Answer B is correct). Oral glutamine is not used for NAI-ALF; it has been studied to aid in the healing of GI fistulas (Answer D is incorrect).

2. **Answer: B**

Osmotic agents are first-line treatment for control of ICP. Although hypertonic saline prevents ICP elevations, the continuous infusion is not used for acute control (Answer A is incorrect). For acute control of ICP elevations, mannitol boluses are used first line provided serum osmolaity is less than 320 (Answer B is correct). Hyperventilation and barbiturates are only used to control ICP elevations when other options have failed (Answers C and D are incorrect).

3. **Answer: C**

This patient has severe acute necrotizing pancreatitis because she has not improved after the first 48 hours, and her CT reveals pancreatitic necrosis involving more than 30% of her pancreas. There appears to be no benefit with using prophylactic antibiotics for patients with necrotizing AP, in reducing either mortality rates or rates of pancreatic and extrapancreatic infections, particularly in more recent studies (Answers A and D are incorrect). Surgical management for sterile necrosis is only recommended if patients have gastric outlet obstruction and/or bile duct obstruction (Answer B is incorrect). For patients with severe acute necrotizing pancreatitis, it is recommended to defer antibiotics unless there is suggestion of infection or if patients have not improved within 7–10 days (Answer C is correct).

4. **Answer: D**

Somatostatin significantly decreases fistula output compared with placebo (Answer A is incorrect). Total parenteral nutrition increases spontaneous closure rates by reducing GI secretions (Answer C is incorrect), and octreotide had a beneficial effect on fistula output in one small study (Answer B is incorrect). Although glutamine has been associated with spontaneous rates of fistula closure, it has been not been associated with reduced fistula output (Answer D is correct).

5. **Answer: B**

Of the possible answers, only alvimopan has been shown to reduce the incidence of ileus postoperatively (Answer B is correct). Metoclopramide has shown mixed results, though the antiemetic properties may be beneficial as adjunctive therapy in POI, and octreotide is not used in the prevention of POI (Answers C and D are incorrect). All opioids can contribute equally to POI (Answer A is incorrect).

6. **Answer: A**

According to the simplified Apfel risk score criteria, this patient has four risk factors for developing PONV (female sex, nonsmoker, history of motion sickness, and perioperative opioids). These risk factors place her at high risk of developing PONV, estimated at greater than 80% (Answers B and D are incorrect). Patients with a high risk of PONV should receive more than two pharmacologic interventions to prevent PONV (Answer A is correct; Answer C is incorrect).

7. **Answer: D**

Frank bloody output from the rectum is more indicative of a lower GI bleed than an UGIB. However, patients with a brisk UGIB may present with bright red blood per rectum. Although a lower GI bleed is more likely, the patient should be initiated on a PPI infusion and undergo an esophagogastroduodenoscopy as soon as possible (Answer D is correct). After the esophagogastroduodenoscopy, the patient should have a colonoscopy. The priority in this patient's case is to evaluate for an UGIB because the finding of "coffee-ground" material on NG lavage suggests that the bleeding source is UGIB

(Answer C is incorrect). Although previous guidelines recommended initiating PPIs before endoscopy, the most recent version does not recommend for or against this practice (Answer A is incorrect). High-dose PPIs should be continued for 48 hours after endoscopy and then followed by twice-daily treatment from days 4–14. (Answer B is incorrect).

8. **Answer: A**

The patient, who presented with signs and symptoms of myxedema coma, was given this diagnosis by the treating team. Of the possible answers listed, only levothyroxine is appropriate for the treatment of myxedema coma (Answer A is correct). Insulin, propylthiouracil, and propranolol play no role in the treatment of myxedema coma (Answers B–D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

The most recent guidelines from the American Association for the Study of Liver Diseases and the U.S. Acute Liver Failure Study Group define ALF as a coagulopathy, usually an INR of 1.5 or more, with any degree of encephalopathy in patients without preexisting liver disease (Answer C is correct). Although jaundice, thrombocytopenia, and leukocytosis can occur in patients with ALF, they are not currently defined as hallmark signs of the disease that exist in all patients (Answers A, B, and D are incorrect).

2. **Answer: A**

Administration of acetylcysteine is recommended in all ALF cases when acetaminophen is suspected as a cause, regardless of the acetaminophen concentration (Answer B is incorrect). Although oral and intravenous formulations have efficacy for the treatment of acetaminophen overdose, the intravenous formulation is recommended when patients have greater than grade I encephalopathy or hypotension or when they cannot tolerate oral therapy (Answers C and D are incorrect). Intravenous acetylcysteine is recommended for most patients who present with liver failure and can be extended beyond the 21-hour regimen, especially if therapy was initiated more than 8 hours after ingestion or baseline concentrations were greater than 300 mg/dL (Answer A is correct).

3. **Answer: D**

Patients with AP should not be kept NPO (Answer A is incorrect). Studies that have compared TPN with enteral feeding in AP have shown that enteral feeding is associated with reduced mortality and infectious complications. Thus, enteral feeding is recommended over TPN for AP, if it is tolerated (Answer B is incorrect). Enteral feeding can be given by either the NJ or the NG route for AP, though the NG route may increase the risk of aspiration. Because this patient has several admissions for aspiration and is thus high risk for aspiration, it is safer to use the NJ route over the NG route (Answer C is incorrect, Answer D is correct).

4. **Answer: C**

Fistula output is defined as high if the output is greater than 500 mL/day, moderate if it is 200–500 mL/day, and low if it is less than 200 mL/day. This patient's fistula output has decreased significantly (Answers A and D are incorrect) from 570 mL/day to 250 mL/day, but it is still not enough to classify her fistula output as low (Answer B is incorrect). Her output has decreased from high to moderate (Answer C is correct).

5. **Answer: B**

In a long-term study of alvimopan for opioid-induced bowel dysfunction, alvimopan was associated with higher rates of myocardial infarction than was placebo. To mitigate this risk, the FDA has limited the use of alvimopan to short-term, inpatient use, and patients cannot receive more than 15 doses (Answer B is correct); however, its use is not contraindicated in patients with a history of myocardial infarction (Answer D is incorrect). The FDA-approved dose is 12 mg twice daily, and there is no requirement for QTc monitoring with alvimopan (Answers A and C are incorrect).

6. **Answer: D**

Dexamethasone and aprepitant should be given before inducing anesthesia for the prevention of PONV (Answers A and C are incorrect). Ondansetron and other serotonin-3 antagonists are most effective if given at the end of surgery (Answer B is incorrect). Droperidol is effective for the prevention of PONV when given at the end of surgery (Answer D is correct).

7. **Answer: A**

H. pylori is a recognized carcinogen and should be eradicated using a 14-day PPI/antibiotic combination (Answer B is incorrect). Patients with an acute UGIB who present with a high-risk bleed should have a diagnostic and therapeutic endoscopy within 24 hours of admission (Answer C is incorrect). Blood transfusions should be administered to keep the hemoglobin concentration greater than 7 g/dL (Answer D is incorrect). Therefore, the only inappropriate treatment option is using octreotide (Answer A is correct).

8. **Answer: B**

Thyroid storm is an uncommon but deadly manifestation of hyperthyroidism; therefore, TSH will be low, whereas T_4 and T_3 will be high (Answer B is correct). Myxedema coma is a manifestation of hypothyroidism; therefore, patients will typically have high TSH and low T_4/T_3. When TSH is high, both T_3 and T_4 are typically low (Answer A is incorrect). Conversely, if TSH is low, both T_3 and T_4 are typically high (Answers C and D are incorrect).

Appendix 1. Most Common or Well-Described Drugs Associated with DILI and the Patterns of Liver Injury

Drug Class	Typical Pattern of Injury
Antibiotics	
• Amoxicillin/clavulanate	• Cholestatic injury
• Isoniazid	• Hepatocellular injury
• Trimethoprim/sulfamethoxazole	• Cholestatic injury, can also be hepatocellular injury
• Fluoroquinolones	• Hepatocellular, cholestatic, or mixed injury
• Macrolides	• Hepatocellular injury
• Nitrofurantoin	• Hepatocellular injury
• Minocycline	• Hepatocellular injury
Antiepileptics	
• Phenytoin	• Hepatocellular, cholestatic, or mixed injury
• Carbamazepine	• Hepatocellular, cholestatic, or mixed injury
• Lamotrigine	• Hepatocellular injury
• Valproate	• Hepatocellular injury, may also cause hyperammonemia
Nonsteroidal anti-inflammatory drugs	• Hepatocellular
Immune modulators	
• Interferon	• Hepatocellular injury
• Anti-TNF agents	• Hepatocellular injury
• Azathioprine	• Cholestatic injury, can also be hepatocellular injury
Herbal medications and dietary supplements	
• Green tea extract	• Hepatocellular injury
• Flavocoxid	• Hepatocellular, cholestatic, or mixed injury
Miscellaneous	
• Methotrexate	• Fatty liver
• Allopurinol	• Hepatocellular or mixed injury
• Amiodarone	• Hepatocellular, cholestatic, or mixed injury
• Androgen-containing steroids	• Cholestatic injury
• Inhaled anesthetics	• Hepatocellular injury
• Niacin (more common with long-acting form)	• Hepatocellular injury
• Sulfasalazine	• Hepatocellular, cholestatic, or mixed injury
• Proton pump inhibitors	• Hepatocellular injury

TNF = tumor necrosis factor.

Information from: Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014;109:950-66.

Supportive and Preventive Medicine

Megan Feeney, Pharm.D., BCCCP

Boston Medical Center
Boston, Massachusetts

SUPPORTIVE AND PREVENTIVE MEDICINE

MEGAN FEENEY, PHARM.D., BCCCP

BOSTON MEDICAL CENTER
BOSTON, MASSACHUSETTS

Learning Objectives

1. Identify the key components of intensive care medicine that can be applied to all critically ill patients.
2. Recommend therapeutic options to prevent stress-related mucosal disease.
3. Recommend therapeutic options to prevent venous thromboembolism in a critically ill patient.
4. Compare therapeutic options for patients with heparin-induced thrombocytopenia.
5. Discuss medications that can be used to comfort a critically ill patient at the end of life.
6. Examine the pharmacists' role in disaster response.
7. Examine the role of social determinants of health in patient outcomes.

Abbreviations in This Chapter

aPTT	Activated partial thromboplastin time
BPS	Behavioral Pain Scale
CDI	*Clostridioides difficile* infection
CPOT	Critical-Care Pain Observation Tool
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
H_2RA	Histamine-2 receptor antagonist
HIT	Heparin-induced thrombocytopenia
ICU	Intensive care unit
LDUH	Low-dose unfractionated heparin
LMWH	Low-molecular-weight heparin
NGT	Nasogastric tube
PF4	Platelet factor 4
Plt	Platelet count
PPI	Proton pump inhibitor
RASS	Richmond Agitation-Sedation Scale
SRMD	Stress-related mucosal disease
SUP	Stress ulcer prophylaxis
VTE	Venous thromboembolism

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. On rounds, you have a "checklist" of interventions that will benefit all critically ill patients in an intensive care unit (ICU). Which interventions would be most effective?
   A. Initiate stress ulcer prophylaxis (SUP) in patients who are admitted to the ICU, and if appropriate, discontinue sedation.
   B. Initiate enteral nutrition, when appropriate, and mechanical venous thromboembolism (VTE) prophylaxis.
   C. If appropriate, initiate sedation interruption, and ensure that patients' heads are elevated 45 degrees above the bed, if not contraindicated.
   D. Assess the need for VTE prophylaxis in patients admitted to the ICU, and initiate an insulin infusion to maintain a blood glucose of 120 mg/dL.

2. Regarding pharmacologic prophylaxis for stress-related mucosal injury, which is most appropriate?
   A. Sucralfate neutralizes gastric pH.
   B. Proton pump inhibitors (PPIs) are superior to histamine-2 receptor antagonists (H_2RAs) in preventing clinically significant bleeding.
   C. Tolerance will occur with continued H_2RA administration.
   D. Antacids are effective when used up to three times daily.

3. A 66-year-old man is admitted to the ICU with abdominal pain, nausea, and altered mental status. He has a history of cirrhosis, atrial fibrillation, chronic kidney diease, and erosive esophagitis. He is intubated and stabilized on the ventilator. A nasogastric tube (NGT) is placed, and the patient is tolerating enteral tube feedings. Which would be best to recommend for preventing stress-related bleeding?
   A. Pantoprazole 40 mg intravenously twice daily.
   B. Cimetidine 300 mg four times daily by NGT.
   C. Famotidine 20 mg intravenously twice daily.
   D. Omeprazole suspension 20 mg once daily by NGT.

4. A 51-year-old woman is admitted to the ICU for hypovolemic shock secondary to severe dehydration. She reports a 5-day history of diarrhea and malaise. She has no recent history of illnesses or contact with health care personnel. Her medical history includes hypothyroidism and gastroesophageal reflux disease. Her medications include levothyroxine 25 mcg orally daily and famotidine 20 mg orally at bedtime. Recently, her primary care physician changed famotidine to omeprazole 20 mg orally at bedtime for increased gastroesophageal reflux disease symptoms. While she is in the ICU, testing for *Clostridioides difficile* infection (CDI) returns positive. Which would be most appropriate regarding PPI use and CDI?

A. PPIs are a potential risk factor for CDI by producing hypochlorhydria and increasing the host susceptibility to infections.
B. Prospective randomized controlled trials have shown that the risk of CDI is associated with PPI use.
C. There is no association between PPI use and CDI risk.
D. Studies reporting on CDI and PPI use have used the same definition of CDI and implemented the same infection control practices.

5. A 50-year-old woman (weight 70 kg) is admitted to the ICU for worsening mental status. Her medical history is significant for hypertension, tobacco use, and osteoporosis. The next morning, she is intubated and stabilized on a ventilator. An NGT is placed. Her current medications include ceftriaxone 2 g intravenously every 12 hours, vancomycin 1250 mg intravenously every 12 hours, acyclovir 800 mg intravenously every 8 hours, famotidine 20 mg by NGT twice daily, and a bowel regimen. Serum creatinine (SCr) is normal. Which would be the most appropriate VTE prophylaxis for this patient?

   A. Intermittent pneumatic compression devices.
   B. Enoxaparin 40 mg subcutaneously daily.
   C. Unfractionated heparin continuous infusion to maintain a therapeutic activated partial thromboplastin time (aPTT).
   D. No VTE prophylaxis at this time.

6. A 34-year-old woman (weight 65 kg) is admitted to the ICU with several upper extremity fractures, a closed-head injury, and a grade 4 liver laceration after a motor vehicle collision. Her medical history is nonsignificant. She is admitted to the ICU on a ventilator after surgery. Her current laboratory values are as follows: sodium (Na) 145 mEq/L, potassium (K) 3.1 mEq/L, chloride 97 mEq/L, carbon dioxide 18 mEq/L, blood urea nitrogen (BUN) 70 mg/dL, and SCr 3.5 mg/dL. Which would be the most appropriate VTE prophylaxis on the day of admission for this patient?

   A. Provide intermittent pneumatic compression devices.
   B. Give enoxaparin 30 mg subcutaneously every 12 hours.
   C. Give fondaparinux 2.5 mg subcutaneously daily.
   D. No VTE prophylaxis is indicated at this time.

7. A 34-year-old man (weight 70 kg) is admitted to the surgical ICU for acute respiratory failure from pancreatitis. He has no pertinent medical history. His current medications include norepinephrine at 0.07 mcg/kg/minute, dexmedetomidine at 0.7 mcg/kg/hour, ampicillin/sulbactam 3 g intravenously every 6 hours, famotidine 20 mg intravenously twice daily, and heparin 5000 units subcutaneously three times daily. On day 3 of his ICU admission, the team suspects heparin-induced thrombocytopenia (HIT). His platelet count (Plt) was 360,000/mm^3 on admission and is 180,000/mm^3 today. The 4Ts score is used to determine the probability of HIT. This patient's 4Ts score is 3 (equating to a low probability of HIT). The team would like to send the heparin–platelet factor 4 (PF4) immunoassay and initiate argatroban. Which is the most appropriate response?

   A. Discontinue all heparin products, but do not initiate argatroban.
   B. Discontinue all heparin products, and initiate argatroban.
   C. Send the heparin-PF4 immunoassay, and continue low-dose unfractionated heparin (LDUH) until the results return.
   D. Do not send the heparin-PF4 immunoassay, and continue LDUH.

8. Which would be the most important group of considerations in a critically ill patient approaching the end of life?

   A. Pain management, tight glucose management, and control of secretions.
   B. Routine vital sign checks, discontinuation of unnecessary medications, and control of secretions.
   C. Pain management, control of secretions, and discontinuation of unnecessary medications.
   D. Discontinuation of unnecessary medications, insertion of a Foley catheter, and treatment of nausea and vomiting.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1–4
    b. Task B: 2, 5
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1–8
    b. Task B: 5, 9, 10, 13, 14
    c. Task C: 1, 3, 5
3. Domain 3: Professional Practice
    a. Task A: 2
    b. Task B: 1, 4, 7

I. KEY ASPECTS IN THE GENERAL CARE OF ALL CRITICALLY ILL PATIENTS

A. The FAST-HUG mnemonic emphasizes important aspects of ICU medicine that can be applied at least daily to all critically ill patients to ensure safe, effective, and efficient care, as described in Table 1 (Crit Care Med 2005;33:1225-9).

Table 1. Key Elements of the FAST-HUG Approach

Element	Importance	Considerations
Feeding	Malnutrition can lead to impaired immune function, in turn leading to increased susceptibility to infection, inadequate wound healing, bacterial overgrowth in the GI tract, and increased propensity for decubitus ulcers	• Initiate enteral feeding (preferred to parenteral nutrition) as soon as possible, typically within the first 24–48 hr after stabilization • (See Fluids, Electrolytes, Acid-Based Disorders, and Nutrition Support chapter for a more in-depth review)
Analgesia	Analgesic and sedative administration optimizes patient comfort and minimizes the acute stress response (hypermetabolism, increased oxygen consumption, hypercoagulability, and alterations in immune function)	• Pain should regularly be assessed with a validated tool such as the Behavioral Pain Scale (BPS) or the Critical-Care Pain Observation Tool (CPOT) • Preemptive analgesia should be considered for invasive or potentially painful clinical procedures • (See Management of Pain, Agitation, and Neuromuscular Blockade in Adult Intensive Care Unit Patients chapter for a more in-depth review)
Sedation		• Sedation should be assessed and reassessed with a validated tool such as the Richmond Agitation-Sedation Scale (RASS) or the Sedation Agitation Scale (SAS) • Maintain light levels of sedation unless the patient has an indication for deep sedation, such as neuromuscular blockade • If appropriate, execute daily sedative interruption • (See Management of Pain, Agitation, and Neuromuscular Blockade in Adult Intensive Care Unit Patients chapter for a more in-depth review)
Thromboembolic prophylaxis	Most ICU patients have at least one risk factor for VTE	• Initiate appropriate prophylaxis, considering VTE and bleeding risks • Mechanical prophylaxis (graduated compression stockings or intermittent pneumatic compression devices) is an alternative nonpharmacologic option in patients at high risk of bleeding
Head of bed elevation	Elevating the head and thorax above bed to a 30–45 degree angle reduces the occurrence of GI reflux and nosocomial pneumonia in patients who are receiving mechanical ventilation	• Where appropriate, ensure patient position periodically throughout the day, especially after procedures that require the patient to lie flat

Table 1. Key Elements of the FAST-HUG Approach *(continued)*

Element	Importance	Considerations
Stress **U**lcer prophylaxis	Critically ill patients develop stress-related mucosal damage, potentially leading to clinically significant bleeding	• Assess and evaluate the patient's risk factors for stress ulcer bleeding • Consider discontinuing acid-suppressive medications when risk factors are no longer present
Glycemic control	Glycemic control is necessary in critically ill patients to decrease the incidence of complications such as decreased wound healing, increased infection risk, and increased risk of polyneuropathy	• Maintaining blood glucose at 140–180 mg/ dL should be considered in the acutely ill patient • Glycemic management protocols should be initiated for persistent hyperglycemia (blood glucose > 180 mg/dL) in critically ill adults • (See Fluids, Electrolytes, Acid-Based Disorders, and Nutrition Support chapter for a more in-depth review)

GI = gastrointestinal; ICU = intensive care unit; VTE = venous thromboembolism.

B. Updated Mnemonic: FAST-HUGS BID (Crit Care Med 2009;37:2326-7; author reply 2327)
S = spontaneous breathing trial
B = bowel regimen
I = indwelling catheter removal
D = de-escalation of antimicrobials

C. MAIDENS: Additional Mnemonic with a Medication Focus (Can J Hosp Pharm 2011;64:366-9)
M = medication reconciliation
A = antibiotics or anti-infectives
I = indications for medications
D = drug dosing
E = electrolytes, hematology, and other laboratory results
N = no drug interactions, allergies, duplications, adverse effects
S = stop dates

D. Daily Checklists
1. Provide a framework of standardization and regulation of interventions in a systematic manner, allowing individuals to assess the presence or absence of the items.
2. Provide structure to important ICU-related interventions in an effort to reduce errors of omission and increase compliance with evidence-based practices to improve outcomes in the ICU patient population (N Engl J Med 2009;360:491-9; N Engl J Med 2006;355:2725-32)
3. Increase identification of drug-related issues (Can J Hosp Pharm 2013;66:157-62; Pharmacy [Basel] 2022 30;10:74)

Patient Case

1. A 68-year-old man (weight 85 kg) is admitted to the ICU for the management of severe hypoxemic respiratory failure associated with community-acquired pneumonia. He is endotracheally intubated and placed on mechanical ventilation. His medical history consists of Child-Pugh class B cirrhosis secondary to alcohol abuse, heart failure, and myocardial infarction. His laboratory values show white blood cell count (WBC) 15 x 10^3 cells/mm^3, Plt 150,000/mm^3, BUN 15 mg/dL, SCr 1.1 mg/dL, K 4.5 mEq/L, glucose 210 mg/dL, international normalized ratio (INR) 1.0, aspartate aminotransferase (AST) 58 IU/mL, and alanine aminotransferase (ALT) 49 IU/mL. His current medications include azithromycin 500 mg intravenously daily, ceftriaxone 1 g intravenously daily, vancomycin 1250 mg intravenously every 12 hours, heparin 5000 units subcutaneously every 8 hours, fentanyl drip at 50 mcg/hour titrated to a Critical-Care Pain Observation Tool (CPOT) score less than 2, midazolam drip at 1 mg/hour titrated to a Richmond Agitation-Sedation Scale (RASS) of 0 to -1, and a regular insulin drip at 1.5 units/hour titrated to maintain blood glucose at 140–180 mg/dL. Currently, on day 3 of his ICU stay, the patient's head is 30 degrees above the bed, his RASS is documented as -4, he is on minimal ventilator settings, and an NGT is placed. As the clinical pharmacist rounding on this patient, you go through the FAST-HUG mnemonic. Which are the best recommendations for the team?
    A. Initiate enteral nutrition by NGT, add SUP, and discontinue fentanyl and midazolam drips.
    B. Initiate enteral nutrition by NGT, discontinue deep venous thrombosis (DVT) prophylaxis, and transition the insulin drip to sliding scale.
    C. Transition the insulin drip to sliding scale, add SUP, and discontinue fentanyl and midazolam drips.
    D. Discontinue fentanyl and midazolam drips, discontinue DVT prophylaxis, and add SUP.

II. STRESS ULCER PROPHYLAXIS

A. Epidemiology of Stress-Related Mucosal Disease (SRMD)
   1. Early studies demonstrated endoscopic evidence of superficial mucosal damage in 75%–100% of patients within 1–2 days after ICU admission.
      a. Few current evaluations are available
      b. Asymptomatic ulceration is likely clinically insignificant (Acta Anaesthesiol Scand 2017;61:216-23; Crit Care Med 1991;19:887-91)
   2. Incidence of clinically significant stress-related bleeding among the critically ill population is 2%–5% (Cureus 2020;12:e8029; Intensive Care Med 2019;45:1540-9)
   3. Stress ulcers and peptic ulcers are differentiated in Table 2

B. Characteristics of SRMD
   1. Several superficial erosive lesions occurring early in the course of critical illness, potentially progressing to deep ulcers
   2. Stress ulcers are diffuse and unamenable to endoscopic therapy; they generally heal over time, without intervention, as the patient's clinical status improves.

Table 2. Stress Ulcers vs. Peptic Ulcers

Stress Ulcers	Peptic Ulcers
Several superficial lesions at the proximal stomach bulb; involves superficial capillaries; results from splanchnic hypoperfusion	Few deep lesions in the duodenum; typically involves a single vessel; results from break in gastric, duodenal, or esophageal lining from the corrosive action of pepsin

C. Pathophysiology of SRMD (N Engl J Med 2018;378:2506-16)
   1. Decreased gastric blood flow and mucosal ischemia are the primary causes of stress ulcer–related bleeding.
   2. Reduced splanchnic blood flow is caused by mechanisms common to critical illness:
      a. Hypovolemia
      b. Reduced cardiac output
      c. Proinflammatory mediator release
      d. Increased catecholamine release
      e. Visceral vasoconstriction
   3. Additional factors leading to stress ulcer–related bleeding:
      a. Decreased gastric mucosal bicarbonate production
      b. Decreased gastric emptying of irritants and acidic contents
      c. Acid back-diffusion
      d. Reperfusion injury that may occur after restoration of blood flow after prolonged periods of hypoperfusion

D. Risk Factors for Stress-Related Bleeding
   1. Studies evaluating risk factors for stress-related bleeding in the presence and absence of SUP are summarized in Table 3.

Table 3. Studies Evaluating Risk Factors for Stress-Related Bleeding

Study	Design and Population	Independent Risk Factors for Bleeding	Notes
N Engl J Med 1994;330:377-81	• Multicenter, prospective cohort study of 2252 ICU patients • Prophylaxis discouraged, except for head injury, burns > 30% of total body surface area, organ transplantation, evidence of peptic ulcer disease, or upper GI bleeding within previous 6 wk • Prophylaxis administered for 674 patients (29.9%); agents included H_2RAs, antacids, sucralfate, prostaglandin analogues, and omeprazole	• Mechanical ventilation ≥ 48 hr • Coagulopathy, defined as Plt < 50,000 cells/mm^3, INR > 1.5, or activated partial thromboplastin time > 2 times control	• Patients with ≥ 2 risk factors had a 3.7% incidence of bleeding vs. 0.1% if risk factors were absent • Most were cardiothoracic patients; extrapolations to other ICU settings potentially inaccurate

Table 3. Studies Evaluating Risk Factors for Stress-Related Bleeding *(continued)*

Study	Design and Population	Independent Risk Factors for Bleeding	Notes
Crit Care Med 1999;27:2812-7	• Multicenter, prospective cohort study of 1200 mechanically ventilated patients • Randomized trial of sucralfate vs. ranitidine for prevention of GI bleeding	• Renal failure (RR 1.16; 95% CI, 1.01–1.32).	• Enteral nutrition and SUP with ranitidine associated with lower incidence of GI bleeding
JAMA Intern Med 2014;174:564-74	• Multicenter, retrospective database study of 35,312 ICU patients • SUP administered with histamine-2 receptor antagonist or PPI for 48 hr	• Age > 50 yr • Male sex • Acute respiratory failure • Shock • Sepsis • Acute kidney injury • Acute or chronic hepatic injury • Neurologic injury • Myocardial infarction • Coagulopathy	• Unable to assess severity of GI bleeding outcomes as events identified by ICD-9 codes
Intensive Care Med 2015;41:833-45	• Multicenter, prospective, cohort study of 1034 ICU patients • Overall, 73% received SUP at some point during ICU admission, most often PPIs	• Renal replacement therapy • Liver disease • Greater severity of illness • Coexisting or acute coagulopathy	

GI = gastrointestinal; ICU = intensive care unit; ICD-9 = *International Classification of Diseases, Ninth Revision*; INR = international normalized ratio; PPI = proton pump inhibitor; SUP = stress ulcer prophylaxis.

Information from: Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med 1994;330:377-81; Cook DJ, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. Crit Care Med 1999;27:2812-7; MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med 2014;174:564-74; Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med 2015;41:833-45.

2. Additional risk factors for SRMD (Am J Health Syst Pharm 1999;56:347-79; *Crit Care Med*. 2024;52(8):e421-e430. J Trauma 1995;39:289-94):
   a. Spinal cord/head trauma
   b. Thermal injury affecting more than 35% of total body surface area
   c. History of GI bleed within the past year
   d. Postoperative transplantation
   e. Ulcerogenic medications (nonsteroidal anti-inflammatory drugs, aspirin, corticosteroids)
3. Elevated intracranial pressure and cerebral vasospasm were found to be additional risk factors for clinically important upper GI bleeds in patients with aneurysmal subarachnoid hemorrhage (*Neurocrit Care*. 2021;35(1):39-45).
4. Enteral nutrition has been suggested as a protective variable (Crit Care Med 2010;38:2222-8; Crit Care 2018;43:108-13)

E. Pharmacologic Therapy for Preventing Stress Ulcers
  1. Antacids
    a. Dose-dependent neutralization of gastric acid
    b. Not recommended for routine use because of frequency of administration (up to every hour), adverse effects (diarrhea, constipation, electrolyte abnormalities), and interactions (interferes with the absorption of some drugs)
  2. Sucralfate (Carafate)
    a. Complexes with albumin and fibrinogen to form a viscous, adhesive substance that adheres to ulcers with a gastric pH less than 4
    b. Not recommended for routine use because of adverse effects (constipation, aluminum toxicity, hypophosphatemia) and drug interactions by method of chelation; frequency of administration further complicates administration of other enteral medications
  3. H_2RAs
    a. Available agents: Cimetidine and nizatidine as oral; famotidine as oral and intravenous (off-label use in SUP)
    b. Competitive blockade of histamine receptors on the basolateral membrane of the parietal cells. In addition, H_2RAs inhibit gastrin secretion to reduce acid production; however, they do not reliably inhibit vagally induced acid secretion.
    c. Alternative pathways (e.g., gastrin, acetylcholine) can be up-regulated in response to the use of H_2RAs, leading to a decrease in gastric pH and explaining the tolerance related to H_2RAs. Tolerance can occur as early as day 2 of H_2RA use (World J Gastrointest Pharmacol Ther 2014;5:57-62; Am J Gastroenterol 1999;94:351-7).
    d. In animal models, H_2RAs may also attenuate reperfusion injury by decreasing interleukin-6 and neutrophil activation, reducing inflammation by enhancing cell-mediated immunity, and acting as a weak free radical scavenger.
    e. Dose-dependent increase in gastric pH
    f. Previous studies of SRMD-related bleeding used either continuous infusion H_2RAs or combined H_2RAs with intermittent antacids to maintain a pH greater than 4. Current practice is to use intermittent administration of H_2RAs without pH monitoring.
    g. All H_2RAs require renal dosing adjustment.
    h. Adverse effects
      i. Mental status changes such as confusion, hallucinations, agitation, and headaches (mainly associated with cimetidine, but reported with famotidine in patients with severe renal failure)
      ii. Thrombocytopenia (occurs over several days from hapten formation; may occur within hours if patient is sensitized)
      iii. Rapid infusion–related hypotension
      iv. Prolongation of corrected QT interval has been reported with famotidine.
      v. Sinus bradycardia
      vi. Risk of nosocomial pneumonia
      vii. Increase in SCr with cimetidine – Competitively inhibits tubular secretion of creatinine
    i. Drug interactions
      i. Cimetidine inhibits cytochrome P450 (CYP) isoenzymes 3A4, 2D6, 2C9, 2C19, and 1A2.
      ii. pH-dependent interactions
  4. PPIs
    a. Available agents: Dexlansoprazole, esomeprazole, lansoprazole, omeprazole (immediate-release capsule FDA approved for SUP), pantoprazole, and rabeprazole
      i. Agents available (off-label) for SUP: Lansoprazole (oral), omeprazole (oral), and pantoprazole (oral, intravenous)
    b. Prodrugs activated in the acidic environment of the stimulated parietal cell inhibiting both histamine-induced and vagally mediated gastric acid by binding and inhibiting active proton pumps
    c. Dose-dependent increase in gastric pH, with maximal activity reached 3 days after initiation
    d. Most trials evaluated the effectiveness of enteral PPIs.

e. Despite short elimination half-lives, PPIs suppress acid secretion for 20 hours or more, permitting once-daily dosing without requiring gastric pH monitoring.
f. Tachyphylaxis does not occur with PPIs.
g. Rebound acid hypersecretion may occur after discontinuation; however, clinical relevance is unknown.
h. Adverse effects
    i. Diarrhea, abdominal pain, constipation, nausea
    ii. Headaches
    iii. Rash
    iv. Interstitial nephritis
    v. Hypomagnesemia (3 months or more of therapy)
    vi. Neurologic effects with high-dose intravenous omeprazole (hearing and vision disturbances)
    vii. Hypophosphatemia and metabolic alkalosis when administered with sodium bicarbonate
    viii. Vitamin B_{12} deficiency
    ix. Increased risk of fractures (hip, waist, and spine)
    x. CDI (definitive cause-effect relationship is not well established)
    xi. Risk of nosocomial pneumonia
i. Drug interactions
    i. All agents are hepatically metabolized by CYP isoenzymes 3A4 and 2C19.
    ii. Omeprazole is an inhibitor of 3A4, 2C19, 2C9, and 1A2.
    iii. Lansoprazole may induce CYP1A2.
    iv. Clinically significant PPI interactions with clopidogrel through CYP2C19 inhibition have not consistently been shown to be important.
    v. pH-dependent interactions

F. Stress-Related Bleeding
1. Endoscopically evident mucosal damage and occult bleeding rates are reported from historical data; more contemporary data are lacking (Table 4).

Table 4. Categories of Stress-Related Bleeding

Outcome	Incidence in ICU Patients	Definition
Endoscopically evident mucosal damage	75%–100%	Superficial lesions identified on endoscopy
Occult bleeding	15%–50%	Presence of guaiac-positive stools or nasogastric aspirate
Overt or clinically evident bleeding	5%–25%	Appearance of coffee grounds in nasogastric aspirate, hematemesis, melena, or hematochezia
Clinically important bleeding	1%–5%	Presence of overt bleeding with hemodynamic instability and/or blood transfusion within 24 hr of the event

2. Clinically important GI bleeding
    a. Most trials define clinically important GI bleeding as overt bleeding accompanied by one of the following:
        i. Decrease in blood pressure of 20 mm Hg within 24 hours before or after GI bleeding episode
        ii. Decrease in blood pressure of 10 mm Hg and increase in heart rate of 20 beats/minute or more on orthostatic change.
        iii. Decrease in hemoglobin of 2 g/dL and transfusion of 2 units of blood within 24 hours of bleeding OR failure of the hemoglobin concentration to increase after transfusion by at least the number of units transfused minus 2 g/dL

  b. Antacids, sucralfate, H_2RAs, and PPIs have all reduced clinically significant SRMD-related bleeding compared with placebo.

3. Studies evaluating interventions for stress-related bleeding are summarized in Table 5.

Table 5. Studies Evaluating Pharmacologic Interventions for Stress-Related Bleeding in Critically Ill Patients

Comparison	Study	Design	Population	CIB	Notes
H_2RA vs Sucralfate	N Engl J Med 1998;338:791-7	Multicenter, randomized, blinded, placebo-controlled	1200 mechanically ventilated ICU patients	• CIB reduced with H_2RA (RR 0.44; 95% CI, 0.21–0.92)	• No difference in in mortality or VAP
	J Crit Care 2017;40:21-30	Meta-analysis, 21 RCTs	3121 ICU patients	• Similar risk of overt or CIB	• Conclusions limited by changes in practice (ventilator bundles, early nutrition)
H_2RA vs PPI	Crit Care 2016;20:120	Meta-analysis, 19 RCTs	2117 ICU patients	• CIB reduced with PPI (RR 0.39; 95% CI, 0.21–0.71; p=0.002)	• No difference in mortality or VAP • Conclusions limited by disproportionate risk factors between patient groups, inconsistent definitions of bleeding, different routes/dosing of agents
	JAMA Intern Med 2014;174:564-74	Retrospective cohort	35,000 mechanically ventilated ICU patients	• CIB increased with PPI (OR 2.24; 95% CI, 1.81–2.76)	• Conclusions possibly limited by selection bias
	Chest 2018;154:557-66	Retrospective cohort	49,576 ICU patients	• CIB increased with PPI (HR 2.37; 95% CI, 1.61–3.5)	• Conclusions possibly limited by selection bias
	"PEPTIC" trial. JAMA 2020; 323:616-26	Open-label, randomized, cluster crossover	28,982 mechanically ventilated ICU patients	• CIB reduced with PPI (RR 0.73; 95% CI, 0.57–0.92) • No difference in mortality (RR, 1.05; 95% CI, 1.00–1.10; p=0.54)	• Possible signal of harm with PPI use; increased mortality with PPI use in cardiac surgery population (RR 1.27; 95% CI, 0.51-1.09) • Poor protocol adherence limits conclusions—only 63.4% in H_2RA group and 82.5% in PPI group exclusively received their assigned therapy

Table 5. Studies Evaluating Pharmacologic Interventions for Stress-Related Bleeding in Critically Ill Patients (*continued*)

Comparison	Study	Design	Population	CIB	Notes
PPI vs placebo	"SUP-ICU" trial. N Engl J Med 2018;379:2199-208	RCTs	3298 ICU patients	• CIB reduced with PPI (RR, 0.58; 95% CI, 0.40–0.86)	• No difference in mortality, infectious complication or myocardial infarction • Did not document enteral nutrition status
	"REVISE" trial. N *Engl J Med.* 2024;391(1):9-20	International, multicenter, randomized, blinded trial	4821 ICU patients receiving mechanical ventilation	• No difference in mortality • CIB decreased with PPI (HR 0.3; 95% CI, 0.19-0.47) • No difference in mortality	• No difference in rate of VAP, CDI, or new RRT • Patient-important GI bleeding less common in PPI group
SUP vs placebo	Intensive Care Med 2020;46:1987-2000	Meta-analysis, 74 RCTs	39,569 ICU patients	• CIB likely reduced with PPI (RR 0.46; 95% CI 0.29–0.93) and H_2RA (RR 0.67; 0.48–0.94) • Possible greater reduction with PPI	• No difference in VAP • Potential for small increase in mortality with PPI

CDI = *C difficile* infection; CIB = clinically important bleeding; H_2RA = histamine-2 receptor antagonist; ICU = intensive care unit; PPI = proton pump inhibitor; RCT = randomized, controlled trial; RRT = renal replacement therapy; SUP-stress ulcer prophylaxis; VAP-ventilator associated pneumonia.

Information from: Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med 1998;338:791-7; Alquraini M, Alshamsi F, Møller MH, et al. Sucralfate versus histamine 2 receptor antagonists for stress ulcer prophylaxis in adult critically ill patients: a meta-analysis and trial sequential analysis of randomized trials. J Crit Care 2017;40:21-30; Alshamsi F, Belley-Cote E, Cook D, et al. Efficacy and safety of proton pump inhibitors for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care 2016;20:120; MacLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA Intern Med 2014;174:564-74; Lilly CM, Aljawadi M, Badawi O, et al. Comparative effectiveness of proton pump inhibitors vs histamine type 2 receptor blockers for preventing clinically important gastrointestinal bleeding during intensive care: a population-based study. Chest 2018;154:557-66; PEPTIC Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group, Alberta Health Services Critical Care Strategic Clinical Network, and the Irish Critical Care Trials Group; Young PJ, et al. Effect of stress ulcer prophylaxis with proton pump inhibitors vs histamine-2 receptor blockers on in-hospital mortality among ICU patients receiving invasive mechanical ventilation: the PEPTIC randomized clinical trial. JAMA 2020; 323:616-26; Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med 2018;379:2199-208; Cook D, Deane A, Lauzier F, et al. Stress ulcer prophylaxis during invasive mechanical ventilation. *N Engl J Med*. 2024;391(1):9-20. Wang Y, Ge L, Ye Z, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: an updated systematic review and network meta-analysis of randomized trials. Intensive Care Med 2020;46:1987-2000.

G. Infectious Complications
  1. Increases in gastric pH promote bacterial overgrowth, potentially leading to infectious complications.
  2. Both H_2RAs and PPIs cause changes in gastric pH; however, PPIs have a greater propensity to maintain a sustained higher pH.
  3. PPIs may also have immunosuppressive effects through the inhibition of neutrophils.
  4. Pneumonia
    a. Meta-analyses have shown lower pneumonia rates with sucralfate than with H_2RAs alone or H_2RAs combined with antacids (JAMA 1996;275:308-14; Crit Care Med 1991;19:942-9).

   b. Meta-analyses have failed to show an association between H_2RAs and PPIs on the risk of pneumonia (Crit Care Med 2013;41:693-705; Am J Gastroenterol 2012;107:507-20; Crit Care Med 2010;38:1197-205); a network meta-analysis conducted and published with the most recent clinical practice guidelines further supports no association between PPIs and risk of pneumonia (*Crit Care Med*. 2016;44(10):1842-1850; *Crit Care Med*. 2017;45(7):1121-1129; *N Engl J Med*. 2018;379(23):2199-2208).
   c. However, patients concurrently receiving enteral nutrition and SUP were found to be at increased risk of pneumonia in a recent systematic review and meta-analysis (*Crit Care*. 2018;22(1):20).
   d. In two large pharmacoepidemiologic cohorts, an increase in the propensity-adjusted odds of pneumonia occurred with PPIs compared with H_2RAs (OR 1.2; CI, 1.03–1.41) in mechanically ventilated patients (JAMA Intern Med 2014;174:564-7) and in patients admitted for cardiac surgery after propensity matching (OR 1.19; CI, 1.03–1.38) (BMJ 2013;347:f5416).
   e. Many of the trials included in these analyses had varying definitions of pneumonia.
5. CDI
   a. A pharmacoepidemiologic cohort study found that CDI rates were significantly higher with PPIs than with H_2RAs (3.8% vs. 2.2%; $p<0.001$) (JAMA Intern Med 2014;174:564-7).
   b. A large retrospective study found PPI use to be an independent risk factor for developing CDI in medical ICU patients (OR 3.11; 95% CI, 1.11–8.74) (J Crit Care 2014;29:696).
   c. No prospective trials have been large enough to evaluate the risk of CDI in ICU patients.
   d. Many published trials have different definitions of CDI, unclear association of antisecretory therapy initiation and CDI diagnosis, and variable infection control practices.
6. In the SUP-ICU trial, there was no difference in infectious adverse events (new-onset pneumonia or CDI).
7. There also were no differences in infectious adverse events (ventilator-associated pneumonia [VAP] in ICU, CDI in hospital) between the pantoprazole and placebo groups in the REVISE trial.
8. SUP duration should be evaluated daily, and SUP should be discontinued as long as no risk factors are present.

H. Pharmacoeconomics
   1. According to the landmark trial comparing H_2RAs with sucralfate, H_2RAs may be more cost-effective because of a reduced incidence of bleeding without an increase in pneumonia rates (N Engl J Med 1998;338:791-7).
   2. Cost-effectiveness models have compared H_2RAs with PPIs with respect to clinically important bleeding and adverse effects (VAP and CDI).
      a. Use of PPI therapy for SUP resulted in a $1250 net cost savings per patient compared with H_2RAs. Univariate sensitivity analysis showed that PPI therapy was not as cost-effective when the probability of VAP rates was altered (Value Health 2013;16:14-22).
      b. Use of H_2RA therapy for SUP resulted in a $1095 net cost savings compared with PPIs. Univariate sensitivity analysis showed that assumptions of pneumonia and bleeding rates were the primary drivers of incremental costs (Crit Care Med 2014;42:809-15).
   3. Initiating SUP in patients at risk and appropriately discontinuing SUP when a patient no longer has any of the risk factors for stress-related bleeding is the best practice for cost minimization.

I. Guideline Recommendations
   1. In 1999, the first guideline from the American Society of Health-System Pharmacists was published (Am J Health Syst Pharm 1999;56:347-79). The guideline recommended that institutions decide on H_2RAs, antacids, or sucralfate according to safety profile, costs, and ease of administration.
   2. In 2008, the Eastern Association for the Surgery of Trauma published a guideline recommending cytoprotective agents, H_2RAs, or PPIs; antacids were not recommended (www.east.org).
   3. In 2014, the Danish Society of Intensive Care Medicine and the Danish Society of Anaesthesiology and Intensive Care Medicine published guidelines suggesting PPIs as the preferred agent (Dan Med J 2014;61:C4811).

4. In 2016, the Surviving Sepsis guidelines recommended PPIs or H_2RAs in patients at risk (Crit Care Med 2017;45:486-552).
5. The 2020 clinical practice guideline for gastrointestinal bleeding prophylaxis for critically ill patients recommended SUP with a gastrointestinal bleeding risk of at least 4% based on several well-studied risk factors. The guidelines made a weak recommendation for PPIs over H_2RAs, with both PPIs and H_2RAs as strongly preferred to sucralfate. (BMJ 2020;368:l6722).
6. The 2024 Society of Critical Care Medicine and American Society of Health-System Pharmacists guideline for the prevention of stress-related GI bleeding in critically ill adults suggests that coagulopathy, shock, or chronic liver disease should be considered risk factors for clinically important upper GI bleeds. These patients should receive SUP compared with no SUP using either PPIs or H_2RAs as first-line agents (*Crit Care Med*. 2024;52(8):e421-e430).
   a. Patients with other risk factors (ie, critically ill but absence of coagulopathy, shock, or chronic liver disease) may be considered at low risk of clinically important stress-related GI bleeding.
   b. Contrary to past guidelines, mechanical ventilation alone is found not likely to be a risk factor and does not necessitate SUP.

Patient Case

Questions 2–4 pertain to the following case.
A 45-year-old woman is admitted to the ICU for severe respiratory failure from community-acquired pneumonia. She is endotracheally intubated and placed on mechanical ventilation. An NGT is placed to begin enteral nutrition. Three days later, she is receiving norepinephrine and vasopressin infusions and appropriate antimicrobial agents. Her WBC is 20 x 10^3 cells/mm^3, Plt 45,000/mm^3, BUN 70 mg/dL, SCr 4.5 mg/dL (baseline 0.9 mg/dL), K 4.5 mEq/L, INR 1.4, AST 30 IU/mL, and ALT 46 IU/mL.

2. Which best reflects this patient's risk factors for stress-related bleeding?
   A. Coagulopathy.
   B. Coagulopathy and shock.
   C. Mechanical ventilation, coagulopathy, acute kidney injury, and shock.
   D. Mechanical ventilation, coagulopathy, acute kidney injury, shock, and enteral nutrition.

3. Which would be most appropriate for preventing stress-related bleeding?
   A. Sucralfate 1 g four times daily by NGT.
   B. Magnesium hydroxide 30 mL every 4 hours by NGT.
   C. Pantoprazole 40 mg intravenously twice daily.
   D. Famotidine 20 mg intravenously daily.

4. One week later, the patient's respiratory status has greatly improved. She has been off sedation and vasopressors for the past 4 days, working with physical therapy, and is now extubated. Her only medications include ceftriaxone, heparin subcutaneously, and SUP. Her current laboratory values are as follows: WBC 6 x 10^3 cells/mm^3, Plt 256,000/mm^3, BUN 10 mg/dL, SCr 1.1 mg/dL, K 4.0 mEq/L, INR 0.8, AST 15 IU/mL, and ALT 10 IU/mL. Which would be the most appropriate recommendation regarding this patient's SUP regimen?
   A. SUP should be continued until hospital discharge.
   B. SUP should be continued until ICU discharge.
   C. SUP should be discontinued now.
   D. SUP should be discontinued once the patient is off antimicrobials.

III. PROPHYLAXIS AGAINST DEEP VENOUS THROMBOSIS OR PULMONARY EMBOLISM

A. Epidemiology
  1. Reported occurrence of DVT is 10%–80% (J Crit Care 2002;17:95-104). Precise incidence in the critically ill population is challenging because of inconsistencies in patient populations, different diagnosis strategies, and variable study methodologies.
  2. DVT rates in the absence of prophylaxis vary, depending on the patient population.
    a. In the absence of prophylaxis: 30% in medical-surgical patients, 50%–60% in trauma patients, up to 80% in orthopedic surgical patients, and 20%–50% in neurosurgical patients (Arch Intern Med 2001;161:1268-79)
    b. A randomized controlled trial of medical-surgical ICU patients receiving pharmacologic prophylaxis found proximal DVT rates of 5%–6% using ultrasonography twice weekly for detection (N Engl J Med 2011;364:1305-14).

B. Risk Factors
  1. Malignancy, previous VTE, immobility, known thrombophilia, recent (1 month or less) surgery or trauma, older age (70 or older), heart or respiratory failure, sepsis, obesity (body mass index of 30 kg/m^2 or more), pregnancy, erythropoiesis-stimulating agents with a hemoglobin of 12 g/dL or more, hormonal therapy, recent transfusions of concentrated clotting factors, central venous lines, and long-distance travel (Chest 2012;141:S195-226)
  2. Additional VTE risk factors in critically ill patients: A single-center prospective cohort (n=261) identified four independent risk factors for ICU-acquired VTE: personal or family history of VTE (multivariate hazard ratio [HR] 4.0; 95% CI, 1.5–10.3; p=0.004), end-stage renal failure (HR 3.7; 95% CI, 1.2–11.1; p=0.02), platelet transfusion (HR 3.2; 95% CI, 1.2–8.4; p=0.02), and vasopressor use (HR 2.8; 95% CI, 1.1–7.2; p=0.03) (Crit Care Med 2005;33:1565-71).
  3. In the critically ill population, there are no validated risk assessment models to estimate the risk of VTE.

C. Prevention of VTE in the General Critically Ill Patient Population
  1. Routine ultrasound screening is not recommended (Chest 2012;141:S195-226).
  2. Prophylactic use of inferior vena cava filters is not recommended (Chest 2012;141:S195-226).
  3. Mechanical VTE prophylaxis should be used in a critically ill patient if the patient is bleeding or at high risk of bleeding. Once the bleeding risk abates, pharmacologic VTE prophylaxis can be initiated.
    a. Intermittent pneumatic compression devices and graduated compression stockings (GCS) significantly reduce the risk of symptomatic VTE compared with no prophylaxis (Chest 2012;141:S195-226).
    b. A Cochrane review evaluated the results from 19 studies of GCS (Cochrane Database Syst Rev 2014;12:1-72).
      i. DVT rates were 9% in the GCS group and 21% in the control group (OR 0.33; $p<0.00001$), and pulmonary embolism rates were 2% in the GCS group and 5% in the control group (OR 0.38; p=0.04).
      ii. The patient population was largely limited to those undergoing orthopedic and general surgery.
    c. Data are limited in medical critically ill patients.

   d. The PREVENT trial randomized 2003 critically ill patients to receive either pharmacological prophylaxis alone or pharmacological prophylaxis with intermittent pneumatic compression devices. A majority of included patients were medical (>75%). The addition of mechanical prophylaxis did not result in a difference in the incidence of proximal lower-limb DVT (adjusted relative risk: 0.89; 95% CI, 0.58–1.36), pulmonary embolism (aRR 0.92; 95% CI, 0.32–2.06), and the composite of lower limb DVT/pulmonary embolism (aRR 1.11; 95% CI, 0.85–1.44) (N Engl J Med 2019;380:1305-15).

4. Either LDUH or low-molecular-weight heparin (LMWH) should be initiated in a critically ill patient over no prophylaxis.
5. The 2018 American Society of Hematology guidelines recommend continuing VTE prophylaxis only while patients remain admitted in the hospital, over continuing extended prophylaxis (Blood Adv 2018;2:3360-92).
6. Randomized trials of VTE prophylaxis in critically ill patients are summarized in Table 6.
7. Recommendations for VTE prophylaxis in trauma patients are summarized in Table 7.
8. Recommendations for VTE prophylaxis in the general and abdominal-pelvic surgical patient are summarized in Table 8.
9. Anticoagulants commonly employed and their usual doses for VTE prophylaxis in nontrauma populations (excluding Obstetrics) are summarized in Table 9.

Table 6. Randomized Trials of VTE Prophylaxis in Critically Ill Patients

Citation	Study Type	Population	Intervention	Screening Methods	VTE Rates	Major Bleeding Rates
N Engl J Med 1996;335:701-7	Single-center	344 patients with major trauma	Enoxaparin 30 mg twice daily vs. LDUH 5000 units twice daily	Venography on days 10–14 and US if VTE suspected	Proximal DVT: 14.7% in LDUH group vs. 6.2% in enoxaparin group; p=0.012 PE: 0% in LDUH group vs. 0.8% in enoxaparin group; p=NR	0.6% in LDUH group vs. 2.9% in enoxaparin group; p=0.12
Am J Respir Crit Care Med 2000;161:1109-14	Multicenter, double-blind	221 MV patients with COPD (169 patients evaluated)	Nadroparin (weight based) SC daily vs. placebo	Weekly US and venography	DVT: 15.5% in nadroparin group vs. 28.2% in placebo group; p=0.045	5.6% in nadroparin group and 2.7% in placebo group; p=0.28
Thromb Haemost 2009;101:139-44	Multicenter, double-blind	1935 patients with severe sepsis receiving drotrecogin alfa (activated)	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily vs. placebo	US on day 4–6	DVT: 5.6% in LDUH group vs. 5.9% in enoxaparin group vs. 7.0% in placebo group; p=NS PE: 0.4% in LDUH group vs. 0.4% in enoxaparin group vs. 0.8% in placebo group; p=NS	NR

Table 6. Randomized Trials of VTE Prophylaxis in Critically Ill Patients (*continued*)

Citation	Study Type	Population	Intervention	Screening Methods	VTE Rates	Major Bleeding Rates
Blood Coagul Fibrinolysis 2010;21:57-61	Single-center, double-blind	156 surgical patients undergoing major elective surgery	LDUH 5000 units SC twice daily vs. enoxaparin 40 mg SC daily	US 5–7 days after surgery and when clinically indicated	DVT: 2.7% in LDUH group vs. 1.2% in enoxaparin group; p=0.51	2.7% in LDUH group vs. 1.2% in enoxaparin group; p=0.48
N Engl J Med 2011;364:1305-14	Multicenter, double-blind	3746 medical-surgical ICU patients expected to remain in the ICU ≥ 3 days (90% medical, 76% MV)	LDUH 5000 units SC twice daily vs. dalteparin 5000 international units SC daily	US 2 days after admission, twice weekly, and as clinically indicated	Proximal DVT: 5.8% in LDUH group vs. 5.1% in dalteparin group; p=0.57 PE: 2.3% in LDUH group vs. 1.3% in dalteparin group; p=0.01	5.6% in LDUH group vs. 5.5% in dalteparin group; p=0.98

COPD = chronic obstructive pulmonary disease; DVT = deep venous thrombosis; LDUH = low-dose unfractionated heparin; MV = mechanically ventilated; PE = pulmonary embolism; NR = not reported; NS = not significant; SC = subcutaneously; US = ultrasonography.

D. Prevention of VTE in the Non-orthopedic Surgical Patient (Chest 2012;141:S227-77)

Table 7. VTE Prophylaxis Recommendations in Trauma Patients

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Low-moderate	Low	LMWH,[a] LDUH,[a] or IPCD (all preferred to no prophylaxis)
High[b]	Low	LMWH[a] is the agent of choice unless contraindicated The American Association for the Surgery of Trauma/American College of Surgeons recommend VTE prophylaxis with enoxaparin, with an empiric dose of 40 mg SC every 12 hr adjusted based on anti-Xa level. Lower doses of 30 mg SC every 12 hr may be considered in patients > 65 years of age, < 50 kg, CrCl 30–60 ml/min or other risk factors for bleeding or drug accumulation (*J Trauma Acute Care Surg* 2022;92:597-604; *J Trauma Acute Care Surg.* 2020;89(5):971-981) LDUH[a] is preferred in patients with a CrCl < 30 mL/min/1.73 m^2

[a] If LDUH or LMWH is contraindicated, mechanical prophylaxis with IPCD is preferred to no prophylaxis in the absence of lower-extremity injury.

[b] Includes acute spinal cord injury, traumatic brain injury, pelvic fracture, long bone fracture, venous injury repair, and spinal surgery from trauma; pharmacologic prophylaxis should be initiated as soon as possible, typically 24–48 hr after the event, but this may depend on the extent of bleeding on head computed tomography.

IPCD = intermittent pneumatic compression device; LMWH = low-molecular-weight heparin.

Table 8. VTE Prophylaxis Recommendations in the General and Abdominal-Pelvic Surgical Patient

Risk Level for VTE	Risk of Bleeding	Prophylaxis
Very low (< 0.5%; Rogers score < 7; Caprini score 0)	Low	Early ambulation
Low (~1.5%; Rogers score 7-10; Caprini score 1 or 2)	Low	IPCD
Moderate (~3.0%; Rogers score > 10; Caprini score 3 or 4)	Low	LMWH, LDUH, or IPCD
	High	IPCD
High (~6.0%; Caprini score ≥ 5)	Low	LMWH or LDUH with elastic stockings or IPCD
	Low with contraindications to LMWH or LDUH	Low-dose aspirin, fondaparinux, or IPCD
	High	IPCD until risk of bleeding abates; then pharmacologic prophylaxis should be initiated

Table 9. Therapeutic Options and Dosing in Nontrauma Populations[a]

Agent	Dose in Patients with Normal Renal Function	Dose in Patients with Renal Impairment[b]	Dose Adjustments in BMI > 40 kg/m_2
Enoxaparin	40 mg SC daily	30 mg SC daily	CrCl > 30 mL/min/1.73 m_2: 40 mg SC every 12 h or 0.5 mg/kg every 12 h CrCl < 30 mL/min/1.73 m_2 (excluding HD, PD, CVVH): 40 mg SC every 24 h
Dalteparin	5000 units SC daily	Specific dosage adjustments have not been recommended; accumulation did not occur in critically ill patients with severe renal insufficiency. (Arch Intern Med 2008;168:1805-12)	7500 units SC daily
LDUH	5000 units SC every 8–12 hr: Choosing between every 8 hr and every 12 hr should be based on the patient's risk of thrombosis and bleeding		7500 units SC every 8 h
Fondaparinux	2.5 mg SC once daily for patients weighing ≥ 50 kg Contraindicated in patients with weight < 50 kg	Contraindicated; however, doses of 2.5 mg SC every 48 hr have been used (Pharmacotherapy 2017;37:1241-48).	5 mg SC once daily

[a]Obstetric populations not included. [b]Estimated CrCl 20–30 mL/min/1.73 m^2.

CrCl = creatinine clearance; CVVH = continuous veno-venous hemofiltration; HD = hemodialysis; LDUH = low-dose unfractionated heparin; PD = peritoneal dialysis; SC = subcutaneous(ly).

E. Considerations for Critically Ill Patients
   1. Inability to communicate symptoms (impaired consciousness) and altered physical examination (edema) make the diagnosis of symptomatic VTE challenging in the critically ill population. Routine screening for VTE with ultrasonography is not recommended.

2. Dosing frequency of LDUH (twice vs. thrice daily): Meta-analyses suggest no difference in thrombosis or major bleeding rates with twice-daily regimens compared with thrice-daily regimens in nonsurgical hospitalized patients (Chest 2011;140:374-81). Most of these patients were not critically ill and had few comorbidities. A more recent observational study using the Premier Healthcare Database compared thrice-daily with twice-daily dosing in 30,800 critically ill patients. No significant differences occurred in VTE rates (6.16 vs. 6.23, p=0.8) or bleeding (0.23 vs. 0.33, p=0.084) in the propensity-matched cohort. VTE and bleeding events were both identified using ICD-9 coding (Pharmacotherapy 2019;39:232-41).
3. Bioavailability of subcutaneously administered drugs is reduced in critically ill patients with the concomitant use of vasoactive drugs or the presence of edema, thereby potentially reducing the effect.
4. A high proportion of critically ill patients have acute kidney injury, which may limit the use of LMWH. Reduced doses of LMWH (Table 9), with or without anti–factor Xa (anti-Xa) monitoring, may be considered depending on risk-benefit assessment; however, LDUH is often preferred in critically ill patients with a CrCl less than 30 mL/min/1.73 m^2, particularly in patients receiving peritoneal dialysis, hemodialysis, or continuous veno-venous hemofiltration.
5. Bleeding
   a. Bleeding rates in critically ill patients vary, depending on the type of pharmacologic prophylaxis.
   b. Patients at high risk of bleeding are often excluded from studies.
   c. Patients at high risk of bleeding with a moderate to high risk of VTE may be considered for mechanical VTE prophylaxis; however, pharmacologic prophylaxis should be reassessed when the bleeding risk is no longer present.
6. Limited evidence exists to guide dosing in the critically ill population with obesity. An inverse relationship between body weight and anti-Xa concentration may exist in patients with obesity; however, the risk of VTE and the optimal anti-Xa concentrations to achieve are unclear. Some clinicians may choose heparin 7500 units subcutaneously every 8 hours over heparin 5000 units subcutaneously every 8 hours in patients with BMI greater than 40 kg/m^2; however, several studies, which were limited by sample size, have failed to demonstrate a clinical benefit (Pharmacotherapy 2016;36:740-8; Hosp Pharm 2016;51:376-81). There is also controversy regarding the optimal approach to VTE prophylaxis with enoxaparin in patients with a BMI greater than 40 kg/m^2; approaches to dosing and anti-Xa level vary significantly because of the varying populations studied.
7. Common strategies include either a fixed dose of 40 mg subcutaneously twice daily or 0.5 mg/kg twice daily. For patients with a BMI greater than 50 mg/m^2, in addition to weight-based dosing, some clinicians use 60 mg subcutaneously twice daily (Ann Pharmacother 2011;45:1356-62; J Pharm Technol 2015;31:282-8).
   a. If using anti-Xa–guided therapy, peak concentrations are typically ordered at steady state; they should be obtained 3 to 5 hours after administration of the third or fourth dose of enoxaparin initiation or dose change. Goal anti-Xa for VTE prophylaxis is 0.2 to 0.4 units/mL (*HCA Healthc J Med*. 2023;4(2):105-109).

F. Oral Anticoagulants for VTE Prophylaxis
1. The only study evaluating direct oral anticoagulants (DOACs) for VTE prophylaxis in critically ill patients was a substudy of extended duration (35-42 days) of betrixaban versus shorter duration (10 ± 4 days) LMWH in critically ill medical patients. Of the 7513 patients in the full cohort, 703 critically ill patients were included in the substudy. Extended-duration betrixaban reduced the rate of VTE at 35-42 days from 7.95% to 4.27% (p=0.042). Major bleeding in the two groups was 1.14% and 3.13% (p=0.07).
   a. These findings should currently be treated as exploratory, given that the full study had predefined statistical stipulations that were unmet (Intensive Care Med 2019;45:477-87).
   b. Betrixaban was removed from the market in April 2020 because of a lack of commercial success.
2. Rivaroxaban is noninferior to standard treatments in other settings such as orthopedic surgery.

3. Rivaroxaban 10 mg orally once daily was compared with enoxaparin 40 mg subcutaneously daily for 10 days, followed by placebo in acutely ill hospitalized patients. The rates of asymptomatic or symptomatic VTE, pulmonary embolism, or death were comparable; however, the bleeding rates were increased in the rivaroxaban group (N Engl J Med 2013;368:513-23). A subsequent study evaluating rivaroxaban 10 mg/day orally with placebo in patients at high risk of VTE demonstrated a decrease in rates of symptomatic VTE (0.18 vs 0.42%; HR 0.44, 95% CI, 0.22-0.89); however, low overall VTE and bleeding event rates limit widespread use. Further studies must identify the populations most likely to benefit from extended prophylaxis (N Engl J Med. 2018;379:1118-27).
4. LMWH is preferred to vitamin K antagonists and DOACs for prophylaxis in critically ill patients (Blood Adv 2018;2:3360-92).

G. Heparin-Induced Thrombocytopenia (Chest 2012;141(2 suppl):495S-530S; *Blood Adv.* 2018;2(22):3360-3392)

1. HIT is a severe, immune-mediated reaction that potentially leads to life-threatening complications such as myocardial infarction, skin necrosis, stroke, and VTE (around 50%–75% of patients with HIT develop symptomatic thrombosis).
2. A rare manifestation is delayed-onset HIT, affecting patients exposed to heparin in the recent past (prior 2 weeks) who present with a new thrombosis and low Plt.
3. Frequency of HIT
   a. Higher in patients receiving unfractionated heparin than in patients receiving LMWH, occurring in 1%–5% of patients versus less than 1%, respectively
   b. Occurs in less than 1% of ICU patients
   c. Higher risk in cardiac or orthopedic surgical patients receiving unfractionated heparin (15%) than in medical patients (0.1%–1%)
4. Alternative causes of thrombocytopenia in critically ill patients include extracorporeal devices, intra-aortic balloon pumps, sepsis, disseminated intravascular coagulation, bleeding, and medications (eg, linezolid, carbamazepine, phenytoin, valproic acid). Plts may decrease after surgery on cardiopulmonary bypass and subsequently recover; however, a secondary decrease in Plt may signal potential HIT.
5. Clinical diagnosis of HIT
   a. Suspected when a patient has a decrease in absolute Plt to less than 150,000/mm^3 or a relative decrease of at least 50% from baseline, skin lesions at injection sites, or systemic reactions after intravenous boluses
   b. Typical onset is 5–10 days after heparin exposure, though onset can be delayed and can occur up to 3 weeks after therapy cessation.
   c. Recent heparin exposure, within the last 90 days, may result in rapid-onset HIT, occurring within hours after rechallenge.
   d. Patients with recent unfractionated heparin/LMWH exposure and a new thrombosis should have their Plt checked before anticoagulant therapy is initiated.
6. Probability of HIT
   a. 4T score
      i. Segregates patients into low, intermediate, and high clinical probability on the basis of four criteria
      ii. Four clinical features incorporated: (1) thrombocytopenia, (2) timing of thrombocytopenia, (3) presence of thrombosis or other clinical sequelae, and (4) other causes of thrombocytopenia
      iii. A low probability 4T score (3 or less) has a high negative predictive value (0.998), whereas an intermediate or high probability score (4 or greater) has a low positive predictive value (0.64 and 0.14, respectively) (Blood 2012;120:4160-7).

   b. HEP (HIT Expert Probability) score
      i. Incorporates more clinical features than the 4T score
      ii. More complex (time-consuming) and evaluation studies limited (not in ICU patients)

7. Laboratory testing
   a. Antigen assays
      i. Depends on the detection of antibody binding by enzyme-linked immunosorbent assays or particle-based immunoassays
      ii. An automated latex immunoturbidimetric assay has been made available. This assay does not require sample batching as is common with the enzyme-linked immunosorbent assays; thus, results can be obtained within 20 minutes.
      iii. Antibody present if sample from patient binds to the heparin-PF4–coated wells, leading to a color-producing reaction. A higher antibody concentration leads to greater color production and a higher optical density reading. Optical density readings of 0.4 or greater are considered positive and indicative of HIT antibodies.
      iv. High sensitivity (greater than 90%) and low to moderate specificity
         (a) Clinically insignificant HIT antibodies are often detected among patients who received heparin 5–100 days earlier.
         (b) Detects a range of immunoglobulin (Ig) A and IgM antibodies that are not pathogenic
   b. Functional assays
      i. Examples: Heparin-induced platelet aggregation (HIPA) and C14 serotonin release assay
      ii. Detect platelet activation in the presence of heparin. Patient serum is mixed with washed platelets from healthy volunteers and low and high concentrations of heparin. In the presence of HIT antibodies, platelets are activated in low concentrations of heparin and detected either visually (HIPA) or using radioactive serotonin (serotonin release assay).
      iii. Advantages: High sensitivity and specificity
      iv. Disadvantages: Technically challenging and not readily available; often send-out laboratory tests with a turnaround time of several days

8. Treatment of HIT (Table 10)
   a. An intermediate or high 4T score should prompt immediate discontinuation of all sources of heparin and initiation of an alternative nonheparin anticoagulant until confirmatory testing is completed.
   b. Parenteral direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin. Some studies support the use of the factor Xa inhibitor fondaparinux for the treatment of HIT, though there are reports of fondaparinux-induced HIT.
      i. Argatroban dosing in the critically ill population (*Crit Care*. 2010;14(3):R90; *Ann Pharmacother.* 2007;41(5):749-754)
         (a) Mean dose in critically ill patients was 0.24 plus or minus 0.16 μg/kg/min and was 0.22 plus or minus 0.15 μg/kg/min in critically ill patients with multiple organ dysfunction.
         (b) A typical starting dose is 2 μg/kg/min; however, consider reduced dosing of 1 μg/kg/min in critically ill patients. In patients with severe liver impairment, consider 0.5 μg/kg/min.
         (c) The target aPTT is 1.5 to 3 times baseline.
      ii. Bivalirudin dosing in the critically ill population (*Pharmacotherapy.* 2006;26(4):452-460)
         (a) Dose reduced to 0.05 to 0.1 mg/kg/h, depending on renal function and bleeding risks
         (b) The target aPTT is 1.5 to 2.5 times baseline.
      iii. Parenteral direct thrombin inhibitors are associated with a higher rate of major bleeding

c. Initiate warfarin once the Plt has recovered and is within normal limits (at least 150,000/mm^3) and after at least 5 days of therapy with an alternative parenteral anticoagulant. Alternatively, conservative warfarin dosing may begin once the Plt is recovering. If a patient is receiving warfarin at the time of HIT diagnosis, reversing with vitamin K is recommended.
    i. Initiation of warfarin before Plt recovery increases the risk of thrombotic complications because of depletion of protein C in the setting of HIT.

d. DOACs are another option that significantly simplify HIT management. Currently, data analyses supporting DOACs for HIT are limited to case series and small observational cohort studies (Thromb Res 2015;135:607-9; Blood 2017;130:1104-13; Am J Cardiovasc Drugs 2022;22:417-24). DOACs are a recommended therapeutic option in the American Society of Hematology 2018 guidelines for VTE management in HIT.
    i. Most of the published data for DOAC use in HIT is with rivaroxaban (*Blood Adv.* 2018;2(2):3360-3392); however, DOAC selection should be based on patient- and drug-specific factors.
    ii. Varying dosing strategies have been described based on the presence of thrombosis and/or platelet recovery

Table 10. Parenteral Agents for the Treatment of HIT

	Argatroban	**Bivalirudin**	**Fondaparinux**
FDA approved for the treatment of HIT	Yes	Yes (percutaneous coronary intervention with HIT)	No
Mechanism of action	Direct thrombin inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor
Elimination half-life	40–50 min	25 min	17–20 hr
Elimination	Hepatobiliary	80% enzymatic 20% renal	Renal
Dosing	2 mcg/kg/min (see above for dosing in the critically ill population)	Unlabeled dose for HIT: 0.15–0.2 mg/kg/hr (see above for dosing in the critically ill population)	Unlabeled dose for HIT: < 50 kg, 5 mg SC daily; 50-100 kg, 7.5 mg SC daily; > 100 kg, 10 mg SC daily
Monitoring	aPTT	aPTT	Anti-Xa concentration
INR elevation	Excessive	Moderate	None

aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia SC = subcutaneous(ly).

Patient Cases

5. A 93-year-old man (weight 45 kg) confined to his bed is admitted from a nursing home with a chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation. He has a history of diabetes and heart failure. His laboratory values are all within normal limits except for BUN 35 mg/dL and SCr 2.8 mg/dL (baseline 0.5). Which would be the most appropriate recommendation for VTE prophylaxis in this patient?
   A. Intermittent pneumatic compression devices.
   B. Enoxaparin 30 mg subcutaneously once daily.
   C. Heparin 5000 units subcutaneously twice daily.
   D. Fondaparinux 2.5 mg subcutaneously daily.

Questions 6 and 7 pertain to the following case.
A 55-year-old man (weight 60 kg) with a medical history of diabetes, hyperlipidemia, and a DVT 4 months ago secondary to lower-extremity trauma is admitted today to the ICU for acute respiratory failure from influenza virus. His current laboratory values are as follows: WBC 13.1 x 10^3 cells/mm^3, Plt 250,000/mm^3, BUN 13 mg/dL, SCr 0.9 mg/dL, INR 1.2, AST 22 IU/mL, and ALT 11 IU/mL. His current medication regimen includes fentanyl and midazolam boluses for pain and agitation, piperacillin/tazobactam, vancomycin, regular insulin infusion, SUP, and a heparin drip. Five days later, the patient remains intubated on the same medications. At this time, his Plt has decreased to 112,000/mm^3, and his BUN and SCr have increased to 45 mg/dL and 2.7 mg/dL, respectively. The team sends a heparin-PF4 immunoassay; however, the results will not return for 48 hours.

6. Which would be the best course of action?
   A. Discontinue the heparin drip, and initiate an argatroban continuous infusion at 0.25 mcg/kg/minute.
   B. Do nothing because the patient has several other reasons to be thrombocytopenic.
   C. Discontinue the heparin drip, and initiate fondaparinux at 10 mg subcutaneously daily.
   D. Do nothing until the heparin-PF4 immunoassay results return.

7. Three days later, both the heparin-PF4 immunoassay and the serotonin release assay return positive, and the patient has a new DVT. The team wants to initiate warfarin. The patient's current Plt is 130,000/$mm^{3.}$ Which would be the most appropriate response?
   A. Discontinue argatroban and initiate warfarin.
   B. Continue argatroban and initiate warfarin.
   C. Warfarin should never be used in patients with HIT.
   D. Warfarin should not be initiated right now.

IV. END-OF-LIFE CARE

A. Clinicians commonly provide end-of-life and palliative care in ICUs.

B. The World Health Organization describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" (Global Atlas of Palliative Care at the End of Life).

C. Goals of Palliative Care
  1. Provides relief from pain and other distressing symptoms.
  2. Affirms life and regards dying as a normal process.
  3. Intends neither to hasten nor postpone death.
  4. Integrates the psychological and spiritual aspects of patient care.
  5. Offers a support system to help patients live as actively as possible until death.
  6. Offers a support system to help the family cope during the patient's illness and in their own bereavement; uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated.
  7. Enhances quality of life, and may also positively influence the course of illness.
  8. Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

D. Categories of Support
  1. Pain management is of paramount importance for comfort and reduction of distress. Providers and families can collaborate to identify the sources of pain and relieve them with drugs and other forms of therapy.
  2. Symptom management involves treating symptoms other than pain such as nausea, thirst, bowel and bladder problems, depression, anxiety, dyspnea, and secretions.
  3. Emotional and spiritual support is important for both the patient and the family in dealing with the emotional demands of critical illness.

E. General Considerations
  1. Minimize or discontinue the use of uncomfortable or unnecessary procedures, tests, or treatments.
  2. Minimize or discontinue the use of routine vital sign checks, patient weights, cardiac or other electronic monitoring, fingersticks, and intermittent pneumatic compression devices.
  3. Consider discontinuing routine blood tests, radiologic imaging, and other diagnostic procedures.
  4. Consider discontinuing all medications not necessary for patient comfort or the medications for which routine vital sign or laboratory monitoring is necessary for safe dosing.
  5. Neuromuscular blocking agents should be discontinued, and their effects allowed to reverse, to best assess the patient's comfort level before withdrawal of life support. If this is not possible due to the delay that paralysis cessation would contribute to withdrawal of life support, best efforts should be made to detect discomfort.

F. Symptom Management
  1. Pain
    a. No evidence supports that unconscious patients do not experience pain.
    b. Opioids are the treatment mainstay for patients with pain at the end of life.
    c. Administer as intermittent intravenous bolus doses or consider escalating to an intravenous continuous infusion if intermittent doses are inadequate for pain and comfort; avoid using subcutaneous or enteral, unless intravenous access is unavailable, because the onset is delayed and absorption may be unpredictable (Crit Care Med 2019;47:1619-26).
    d. Bolus and titrate infusion to control labored respirations; specific dosages of medications are less important than the goal of symptom relief. Optimal dose is determined by assessing the patient and rapidly increasing the dose as needed until symptoms are no longer present. Dose is determined by symptom relief and adverse effects (excessive sedation, respiratory depression).

- e. Suggested goals include keeping the respiratory rate at or below 30 breaths/minute and keeping the patient pain free. Pain assessment should include using the visual analog scale, the BPS, or CPOT (see the Management of Pain, Agitation, Delirium and Neuromuscular Blockade in Adult Intensive Care Unit Patients chapter for further details on these scales). Vital signs alone should not be used for pain assessment.
- f. Never use neuromuscular blocking agents to treat pain.
- g. Morphine is most commonly used; hydromorphone and fentanyl are alternatives.
  - i. Morphine should be used cautiously in patients with decreased renal clearance, even at the end of life, to avoid the risk of accumulation of neuroexcitatory metabolites.
- h. Tolerance may develop over time.
- i. Pain can be improved with correct dosing and titration without causing respiratory depression or hastening death (Chest 2004;126:286-93; Crit Care Med 2004;32:1141-8; JAMA 1992;267:949-53).

2. Dyspnea
   - a. Common symptom in patients at the end of life
   - b. Individualize therapy based on underlying cause, patient’s level of consciousness, and level of sedation.
   - c. Oxygen may be used for patients with hypoxia. Corticosteroids, bronchodilators and diuretics may also be useful (Crit Care Med 2008;36:953-63).
   - d. Opioids are the first-line therapy. Opioids reduce oxygen consumption, ventilation, and perception of dyspnea (J Palliat Med 2012;15:106-14).
   - e. No benefit with benzodiazepines unless anxiety is present (Cochrane Database Syst Rev 2010;1:CD007354)
3. Anxiety/agitation/delirium
   - a. Symptoms at the end of life can relate to acute or chronic anxiety, delirium, or terminal delirium.
   - b. Nonpharmacologic treatments for agitation and anxiety can include frequent reorientation to the environment and reduction in noise and other bothersome or stimulating environmental factors.
   - c. Haloperidol is an effective agent for delirium-induced agitation, is available as an intravenous injection, and is less sedating than other agents (Crit Care Med 2008;36:953-63). Intravenous haloperidol may be used without electrocardiographic (ECG) monitoring because the benefits outweigh the risks of prolonged corrected QT interval, given the goals of care.
   - d. Benzodiazepines (midazolam and lorazepam):
     - i. Benzodiazepines are the agents of choice for anxiety. Dose is determined by assessing the patient and increasing the dose as needed (lower initial doses intermittently and titration with frequent assessment).
     - ii. Determining what would be perceived as an acceptable level of sedation with the patient and/or family or surrogate decision-maker is important before initiating sedatives.
     - iii. Tolerance may develop over time.
4. Fever
   - a. Acetaminophen is an effective therapy for improving comfort and decreasing the incidence of fever. If the patient cannot swallow, this agent may be administered per rectum. If neither enteral nor rectal access are available, acetaminophen may be administered intravenously.
   - b. A nonsteroidal anti-inflammatory drug may be used when acetaminophen is ineffective.
   - c. Dexamethasone, which is also known to have antipyretic properties, can be considered.
5. Nausea and vomiting
   - a. Evaluate the patient and determine whether any possible underlying causes (medications, uremia, gastroparesis, and intestinal or gastric obstruction) can be removed or eliminated.
   - b. Agents to consider for symptomatic relief include metoclopramide, haloperidol, risperidone, ondansetron, and dexamethasone.

   c. Lorazepam can be considered as an adjunct, especially with anticipatory vomiting.
   d. Use of more than one agent from different classes may be necessary for symptom relief.
6. Cough
   a. Excessive coughing can lead to exacerbation of dyspnea and spells of nausea and vomiting, in addition to disturbing sleep and exacerbating pain.
   b. Non-opioid antitussives such as benzonatate and dextromethorphan may be considered.
   c. All opioids have intrinsic antitussive action by inhibiting the brain stem cough center; however, if the patient is receiving an opioid for other reasons, adding another opioid has not shown additional benefit.
   d. For refractory cough, consider nebulized lidocaine.
7. Secretions
   a. Near the end of life, the ability to clear oral and tracheobronchial secretions diminishes.
   b. Secretions are usually too low in the tracheobronchial tree for gentle oral suctioning to help, and suctioning can be disturbing.
   c. The treatment mainstay includes anticholinergic and antimuscarinic medications.
      i. Glycopyrrolate (0.2 mg intravenously or subcutaneously every 4-8 hours as needed) or atropine (1% ophthalmic solution 2 drops sublingually every 4 hours as needed) should be used for acute symptoms.
      ii. Scopolamine and atropine cross the blood-brain barrier and can be more sedating than glycopyrrolate.
      iii. The scopolamine patch is more gradual in onset (12 hours).
      iv. More than 1 scopolamine patch may be used for unrelieved symptoms.

Patient Case

8. An 88-year-old woman is admitted to the ICU for decompensated heart failure, and uncontrollable pain from the rib fractures she had 1 month ago from a fall. This is her fourth admission to the ICU in the past 5 months. Speaking with her, you find that she wishes not to be resuscitated or intubated but only to be comfortable. Her blood pressure is currently 119/70 mm Hg, heart rate 120 beats/ minute, and respiratory rate 55 breaths/minute. Her pain is 9/10 using the Behavioral Pain Scale (BPS). In a meeting with the patient's family, all members agree that they do not want to see her suffer any longer. It is decided to initiate a morphine drip at 2 mg/hour. Titration parameters include giving a bolus dose equivalent to the current rate and increasing the infusion by 25% to maintain a score of 3 (no pain) using the BPS. Her laboratory values are all within normal limits, including BUN 10 mg/dL and SCr 0.6 mg/dL. The nurse taking care of the patient believes that the titration parameters are too aggressive. Which would be the most appropriate change in titration parameters?
   A. Change the parameters to increase the morphine drip when the patient has signs of discomfort, such as an increase in blood pressure or heart rate.
   B. Discontinue titration parameters, keeping the morphine infusion at the current rate.
   C. Discontinue titration parameters, keeping the morphine infusion at the current rate and adding a midazolam infusion at 2 mg/hour.
   D. Do not change the titration parameters at this time; however, assess the patient's response after the first dose increase.

V. DISASTER MANAGEMENT

A. The Federal Emergency Management Association (FEMA) defines a *disaster* as any occurrence that results in property damage, deaths or injuries to a community; this occurrence encompasses events ranging from natural or weather events, infectious outbreaks, chemical or radiation releases, terrorist attacks or threats, mass violence, transportation accidents, to technological disasters (https://training.fema.gov/programs/emischool/el361toolkit/glossary.htm)

B. Disaster planning often centers on emergency management; however, a critical care disaster management plan is critical to supporting the influx of critically ill patients who may present for care because of such events (Crit Care Clin.2019 Oct;35(4):551-562.)
   1. Emergency management consists of 4 phases
      a. Preparedness
      b. Response
      c. Mitigation
      d. Recovery
   2. Disaster risk is dependent on the geographic area and institution; a hazard vulnerability analysis (HVA) should be completed annually to identify disaster risks and prioritize mitigation strategies (CDC Hospital All-Hazards Self-Assessment, www.cdc.gov/orr/readiness/resources/healthcare/documents/hah_508_compliant_final.pdf)
   3. Many resources are available to assist in the event of disaster
      a. National Incident Management System (NIMS)—provides guidance to private and public sectors on resource management, command and coordination, and communications and information management for disasters
      b. U.S. States Department of Homeland Security (DHS)
      c. U.S. Department of Health and Human Services (HHS)
         i. Operates the Strategic National Stockpile (SNS), which stores medications and supplies throughout the country to enable rapid dissemination on federal instruction; stocked medications include antibiotics, antivirals, chemical antidotes, antitoxins, vaccines
         ii. Appoints the Assistance Secretary for Preparedness and Response (ASPR) who creates the Technical Resources, Assistance Center and Information Exchange (TRACIE), which contains recommendations for many disasters situations
      d. Local and State Public Health Departments—provide disaster response training for healthcare providers
      e. FEMA—coordinates disaster response in events where local and state response may be overwhelmed
   4. An interprofessional approach to disaster response is key; pharmacists are essential in many elements (Am J Health Syst Pharm 2004;61:1167-75)
      a. Response integration
         i. Ensure appropriate use of medications
         ii. Recognition of bioterrorism events and associated treatments
         iii. First aid and advanced cardiovascular life support skills
         iv. Patient triage and counseling
         v. Interdisciplinary education
      b. Patient management
         i. Drug therapy selection and management
         ii. Patient education regarding therapies, discouraging personal stockpiles and self-treatment
         iii. Ensure continuity of care for chronic disease states via collaborative practice agreements
         iv. Point of care testing and treatment

        v. Vaccine administration
        vi. Telehealth and telepharmacy services
    c. Medication supply
        i. Identify necessary antidotes, critical medications and alternatives, as well as necessary par levels
        ii. Ensure proper preparation and handling of medications
        iii. Maintain effective distribution systems
        iv. Compile accurate therapeutic and patient records
    d. Policy coordination
        i. Develop diagnosis and treatment guidelines and/or policies
        ii. Coordinate efforts with local and state health departments
        iii. Incorporate medication expertise in policy decisions at local and state level
    e. While pharmacists are well-suited to perform the aforementioned tasks, in a disaster response it is also necessary to consider which tasks would most benefit from pharmacist input and which tasks may be delegated to other healthcare professionals

VI. SOCIAL DETERMINANTS OF HEALTH

A. Social determinants of health (SDoH) are environmental conditions that impact morbidity, mortality, and quality-of-life. SDoH encompass five domains of modifiable and non-modifiable factors (Healthy People 2030, HHS, Office of Disease Prevention and Health Promotion, https://health.gov/healthypeople):
    1. Economic stability—employment, food insecurity, housing instability, poverty
    2. Education access and quality—early childhood development and education, higher education enrollment, high school graduation, language and literary
    3. Health care access and quality—access to health services and primary care, health literacy
    4. Neighborhood and built environment—access to foods that support a healthy diet, crime and violence, environmental conditions, housing quality
    5. Social and community context—civic participation, discrimination, incarceration, social cohesion, culture, family

B. Recognizing and addressing SDoH in critically ill patients has the potential to positively impact health care outcomes and costs by identifying opportunities for societal improvement (HHS, Office of the Assistant Secretary for Planning and Evaluation. Building the Evidence Base for Social Determinants of Health Interventions, https://aspe.hhs.gov/reports/building-evidence-base-social-determinants-health-interventions)
    1. Some professional societies, such as the American Thoracic Society and American Heart Association, recommend training of clinicians to facilitate patient screening for SDoH; however, formal curricula and screening tools are lacking (Ann Am Thorac Soc 2017;14:814-26)
    2. Engaging patients from various backgrounds in research is also critical for identifying barriers to care and potential interventions to address these gaps, as well as to identify other population differences
    3. ICU recovery clinics are in an excellent position to pave the way towards addressing SDoH by engaging with patients and caregivers about the challenges they face in post-ICU care

C. Studies evaluating SDoH in the critically ill population are limited and often rely on claims data for their conclusions; it is often difficult to identify the specific SDoH associated with a particular outcomes because different SDoH are tied closely together
   1. A retrospective evaluation of older adults admitted to the ICU demonstrated a greater risk for functional and cognitive decline in patients with dual Medicare–Medicaid coverage compared with those with Medicare with supplemental insurance, suggesting opportunities for improved allocation of rehabilitation resources and post-ICU care (Ann Intern Med 2022;175:644-55). Other studies reinforce this finding, indicating uninsured patients are less likely to receive common critical care procedures (Am J Respir Crit Care Med 2011;184:809-15).
   2. Neighborhood socioeconomic disadvantage and lower socioeconomic status have similarly been associated with higher disability burden after ICU discharge (Chest 2016;150:829-36; Crit Care Med 2022;50:733-41; Intensive Care Med 2018;44:2025-37)
   3. Lower individual socioeconomic status has also been associated with increased health care use and mortality (Crit Care Med 2019; 47:e512-21; J Intensive Care Med 2021;36:828-37)
   4. Members of minority groups are demonstrated to experience higher mortality and disparate end of life care (e.g., less likely to use hospice, fewer advanced directives, less comfort-directed care) (Lancet Respir Med 2017;5:E11-2; Ann Am Thorac Soc 2016;13:2184-9)

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

The mnemonic FAST-HUG stands for **F**eeding, **A**nalgesia, **S**edation, **T**hromboembolic prophylaxis, **H**ead of bed elevation, stress **U**lcer prophylaxis, and **G**lycemic control. Using this mnemonic as a checklist every day for each critically ill patient will help maximize therapeutic interventions and promote patient safety. This patient would benefit from receiving enteral nutrition (an NGT is already placed and he has a working GI tract), interrupting the sedative (current RASS score is above the designated goal), and adding SUP (risk factors include cirrhosis) (Answer A is correct). Critically ill patients with risk factors for VTE should remain on VTE prophylaxis (Answers B and D are incorrect); moreover, sliding-scale insulin should be initiated when the patient is not critically ill and once the glucose is stable (less than 180 mg/dL), adding another reason why Answer B is incorrect and making Answer C incorrect.

2. Answer: B

Factors placing critically ill patients at risk of clinically important stress-related bleeding are shock, chronic liver disease, or coagulopathy (Plt less than $50 \times 10_3/\mu L$, INR greater than 1.5, or aPTT greater than 2 times the control). This patient has coagulopathy as well as septic shock, as evidenced by end-organ dysfunction and acute kidney injury (Answer A is incorrect; Answer B is correct). Answers C and D are incorrect because mechanical ventilation is no longer considered a risk factor for stress-related upper GI bleeding.

3. Answer: D

Antacids are not recommended for routine use because of their frequency of administration, adverse effects, and interactions (Answer B is incorrect). In a large randomized controlled trial, sucralfate was inferior to H_2RAs in preventing clinically significant bleeding from SRMD and is generally not recommended because of its adverse effect profile (Answer A is incorrect). Proton pump inhibitors are no better than H_2RAs in preventing SRMD and may be associated with increased infectious complications, including CDI (Answer D is correct). Meta-analyses have favored PPIs to H_2RAs for GI bleeding; however, the individual trials included lacked methodological quality (Answer C is incorrect).

4. Answer: C

Once the risk factors are no longer present, SUP should promptly be discontinued (Answer C is correct). This patient no longer has risk factors (coagulopathy, shock, or chronic liver disease). In addition, there is no evidence that SUP should be continued until hospital or ICU discharge or when antimicrobial therapy is complete (Answers A, B, and D are incorrect).

5. Answer: C

This patient has several risk factors for VTE, including immobility and respiratory failure, making heparin 5000 units subcutaneously twice daily appropriate for VTE prophylaxis (Answer C is correct). Neither enoxaparin nor fondaparinux is appropriate for this patient, who has acute kidney injury with an estimated CrCl of less than 20 mL/minute/1.73 m^2 (Answers B and D are incorrect). Additionally, VTE prophylaxis with fondaparinux is contraindicated in patients less than 50 kg. Intermittent pneumatic compression would be insufficient in a patient with no contraindication to pharmacologic prophylaxis (Answer A is incorrect).

6. Answer: A

Diagnosing HIT is difficult in a critically ill patient because there are many alternative causes of thrombocytopenia. Clinical assessment is essential in diagnosing HIT because of the immediate need for treatment and the delay in laboratory testing (Answers B and D are incorrect). Clinically, this patient has had a greater than 50% decrease in Plt within 5 days of receiving heparin. The calculated 4Ts score is 5 (2 points for Plt decrease by greater than 50%, 2 points for a clear onset at days 5–10, and 1 point for other possible causes of thrombocytopenia. This score is an intermediate probability for HIT. In managing suspected HIT, first ensure that all forms of heparin are discontinued, including flushes and heparin-coated catheters. Next, initiate an alternative form of anticoagulation. Direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin (Answer A is correct). Factor Xa inhibitors have been used to manage HIT; however, they would not be best in this patient, who has acute kidney injury (Answer C is incorrect).

7. Answer: D

Warfarin can be initiated (Answer C is incorrect) once the Plt has recovered to at least 150,000/mm^3 and after at least 5 days of therapy with an alternative anticoagulant (Answer D is correct). Because this patient's Plts have not reached 150,000/mm^3 and only 3 days of argatroban have been completed, warfarin therapy should not be initiated at this time (Answers A and B are incorrect). Argatroban should be continued, and warfarin may be considered after 5 days of therapy and once the Plt has recovered (Answer B is incorrect).

8. Answer: D

Up to 50% of seriously ill hospitalized patients have moderate or severe pain. Opioids are the treatment mainstay for patients with pain and dyspnea at the end of life. Assessing pain in the ICU can be particularly challenging because many patients have impaired cognition and communication. Vital signs alone should not be used for pain assessment (Answer A is incorrect). Evidence suggests that pain can be improved with correct dosing and titration (Answers B and C are incorrect) without causing respiratory depression or hastening death (Answer D is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The FAST-HUG mnemonic can serve as a checklist for every patient admitted to the ICU. Every patient should be assessed for a sedation interruption to minimize sedative exposure and maintain a light level of sedation (Answer C is correct). To decrease the risk of nosocomial pneumonia, each patient should have his or her head elevated 30–45 degrees above the head of the bed (Answer C is correct). Enteral nutrition should be initiated as soon as possible – typically, once the patient is stabilized; however, thromboprophylaxis should be initiated in every patient, using pharmacologic agents preferentially to mechanical prophylaxis (Answer B is incorrect). Stress ulcer prophylaxis should only be initiated in patients who have risk factors and should be discontinued once the risk factors no longer exist (Answer A is incorrect). Insulin infusions should be initiated if blood glucose readings exceed 180 mg/dL (Answer D is incorrect).

2. Answer: C

Sucralfate forms a protective barrier over the surface of the stomach, reducing exposure to acidic gastric contents; therefore, sucralfate does not affect gastric pH (Answer A is incorrect). Compared with H_2RAs, PPIs appear more effective at reducing gastric acidity, but no well-conducted trial has shown PPIs superior in preventing clinically significant bleeding (Answer B is incorrect). Tolerance to any H_2RA may occur, but not to PPIs (Answer C is correct). Antacids have some effect on reducing stress ulceration, provided the gastric pH is kept around 3.5, but frequent dosing (up to every 2 hours) is required to achieve this goal, making their use impractical (Answer D is incorrect).

3. Answer: D

The patient has an indication for SUP (cirrhosis). He has an NGT in place and is tolerating tube feedings, indicating a functioning gut; therefore, intravenous therapy is not required (Answers A and C are incorrect). The patient has erosive esophagitis, for which a PPI will be more effective than an H_2RA (Answer B is incorrect). Omeprazole suspension is effective in preventing SRMD; therefore, an omeprazole suspension would be most appropriate for this patient (Answer D is correct).

4. Answer: A

Proton pump inhibitors are potent inhibitors of gastric acid production and are the drug of choice for gastroesophageal reflux disease. To date, the only prospective randomized controlled trial to evaluate CDI risk with PPI use found no difference between PPI and placebo; however, this was an underpowered secondary end point, and several cohort studies have found an association. (Answer C is incorrect). All published trials assessing the risk of CDI with PPI use have been limited by the inconsistent definitions of CDI and the variable infection control practices (Answer D is incorrect). Gastric juice is strongly bactericidal for microorganisms. Proton pump inhibitors are commonly used to increase the gastric pH; therefore, they act as a potential risk factor for CDI (Answer A is correct).

5. Answer: B

Low-dose unfractionated heparin or LMWH should be initiated for VTE prophylaxis in a critically ill patient over no prophylaxis (Answer D is incorrect). Intermittent pneumatic compression devices would be insufficient prophylaxis in a patient with several risk factors for VTE (Answer A is incorrect). A continuous infusion of heparin is inappropriate for preventing VTE (Answer C is incorrect). Enoxaparin may be used for VTE prophylaxis in a critically ill patient with stable renal function (Answer B is correct).

6. Answer: A

This patient had a closed-head injury, placing her at high risk of VTE (Answer D is incorrect). She is at high risk of major bleeding and acute kidney injury; therefore, a LMWH or a factor Xa inhibitor would not be best for her (Answers B and C are incorrect). Mechanical prophylaxis with intermittent pneumatic compression devices is preferred to no prophylaxis in the absence of lower-extremity injury until the bleeding risk is no longer present (Answer A is correct).

7. Answer: D

Clinical assessment is essential in diagnosing HIT because of the immediate need for treatment and the delay in laboratory testing. Although this patient's Plt did decrease by 50%, the characteristic onset of the Plt decrease in HIT is 5–10 days after heparin initiation.

Clinical prediction rules to help determine the probability of HIT (e.g., 4Ts score) have been developed. Patients with a low 4Ts score (0–3) have a very low probability of HIT (Answer D is correct). Direct thrombin inhibitors are the agents of choice for anticoagulation in acute HIT because they have no cross-reactivity with heparin. Initiating these agents in those with a low probability of HIT could lead to an unnecessary increase in bleeding risk (Answer B is incorrect). If the 4T score revealed an intermediate or high risk of HIT, the first step would be to ensure that all forms of heparin are discontinued, including flushes and heparin-coated catheters (Answer C is incorrect). The next step would be to initiate an alternative form of anticoagulation (Answer A is incorrect).

8. Answer: C

General considerations in the critically ill patient at the end of life include minimizing uncomfortable or unnecessary procedures, tests, and treatments, including fingersticks, Foley catheters, and routine vital signs (Answers A, B, and D are incorrect). Symptom management of pain and anxiety, fever, cough, secretions, nausea and vomiting, and delirium should be considered in the dying patient (Answer C is correct).

Shock Syndromes I

Gretchen L. Sacha, Pharm.D., FCCM, BCCCP

Cleveland Clinic
Cleveland, Ohio

SHOCK SYNDROMES I

GRETCHEN L. SACHA, PHARM.D., FCCM, BCCCP

CLEVELAND CLINIC
CLEVELAND, OHIO

Learning Objectives

1. Distinguish between the various shock syndromes on the basis of a patient's clinical and hemodynamic parameters.
2. Interpret hemodynamic data from monitoring devices and markers of perfusion.
3. Devise a treatment strategy for when to use intravenous fluids and/or vasopressors in a patient with shock.
4. Develop a treatment pathway for the care of patients with sepsis or septic shock that incorporates current evidence and the Surviving Sepsis Campaign guideline recommendations.

Abbreviations in This Chapter

AVP	Arginine vasopressin
Ca_{O_2}	Arterial oxygen content
CO	Cardiac output
CVP	Central venous pressure
D_{O_2}	Oxygen delivery
Hgb	Hemoglobin
ICU	Intensive care unit
IVC	Inferior vena cava
LV	Left ventricular
LVOT VTI	Left ventricular outflow tract velocity time integral
MAP	Mean arterial pressure
O_2ER	Oxygen extraction ratio
PAC	Pulmonary artery catheter
P_{CO_2}	Partial pressure of carbon dioxide
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PLR	Passive leg raising (test)
PPV	Pulse pressure variation
PRBC	Packed red blood cell
PVR	Pulmonary vascular resistance
RV	Right ventricular
SBP	Systolic blood pressure
SCr	Serum creatinine
Scv_{O_2}	Central venous oxygen saturation
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
St_{O_2}	Tissue oxygen saturation
SV	Stroke volume
Sv_{O_2}	Venous oxygen saturation
SVR	Systemic vascular resistance
SVV	Stroke volume variation
V_{O_2}	Oxygen consumption

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1 and 2 pertain to the following case.
An 80-year-old woman presents to the intensive care unit (ICU) with septic shock caused by an *Escherichia coli* urinary tract infection. Pertinent vital signs on admission are as follows: blood pressure 80/40 mm Hg, heart rate 155 beats/minute with a rhythm of atrial fibrillation, respiratory rate 26 breaths/minute, and temperature 105.8°F (41°C). On physical examination, the patient is weak, lethargic, and confused. Pertinent laboratory values are as follows: sodium (Na) 155 mEq/L, potassium (K) 3.6 mEq/L, serum creatinine (SCr) 1.8 mg/dL, and lactate 4.2 mmol/L.

1. Which clinical symptoms and physiologic variables most likely indicate that this patient has a shock syndrome?
   A. Fever, lethargy, and tachycardia.
   B. Hypotension, fever, and tachypnea.
   C. Hypotension, confusion, and hyperlactatemia.
   D. Tachypnea, fever, and hyperlactatemia.

2. Which variable is most likely contributing to impaired oxygen delivery (D_{O_2}) to the patient's end organs?
   A. Serum lactate.
   B. Atrial fibrillation.
   C. Acute kidney injury.
   D. Fever.

3. A 62-year-old woman (weight 119 kg) develops ventilator-associated pneumonia in the setting of prolonged intubation after aortic valve replacement surgery. Her pneumonia is complicated by septic shock, and she is given 2 L of 0.9% sodium chloride and 1 L of 5% albumin for resuscitation and initiated on norepinephrine. Her laboratory values are as follows: Na 144 mEq/L, chloride (Cl) 110 mEq/L, K 3.8 mEq/L, bicarbonate 18 mEq/L, SCr 1.8 mg/dL, arterial pH 7.28, and albumin 3.2 g/dL. Having

determined that the patient is still fluid responsive, you would like to give another fluid bolus. Which fluid is best for the fluid bolus?

A. 0.9% sodium chloride.
B. 5% albumin.
C. 6% hydroxyethyl starch.
D. Lactated Ringer's solution.

4. A 48-year-old man (weight 82 kg) presents to the medical ICU for septic shock secondary to a urinary tract infection. His medical history is significant only for hypertension. The patient has an initial mean arterial pressure (MAP) of 58 mm Hg and a lactate concentration of 4.8 mmol/L. The patient is initiated on broad-spectrum antimicrobials, has a central venous catheter placed in his right subclavian vein, and is resuscitated with quantitative resuscitation. He receives 2 L of 0.9% sodium chloride total and 2 L of lactated Ringer's solution, and he is initiated on norepinephrine. Three hours after presentation, his current pertinent vital signs, hemodynamic parameters, and laboratory values are as follows: MAP 68 mm Hg on norepinephrine 8 mcg/minute, central venous pressure (CVP) 10 mm Hg, central venous oxygen saturation (Scvo$_2$) 72%, urinary output 0.2 mL/kg/hour, and lactate 4.6 mmol/L. Which is the next best step for the patient's hemodynamic therapy?

A. Continue current therapy.
B. Increase the norepinephrine dose.
C. Give 1 L of 0.9% sodium chloride.
D. Initiate dobutamine.

5. An 82-year-old man is admitted to the surgical ICU after an exploratory laparotomy and small bowel resection for a small bowel obstruction that was complicated by fecal peritonitis and hypotension. The patient received 2 L of lactated Ringer's solution, 500 mL of 5% albumin, and 500 mL of 6% hydroxyethyl starch in the operating room, but vasopressors were never initiated. He remains intubated and mechanically ventilated, requiring a 90% fraction of inspired oxygen (Fio$_2$), with the following vital signs: heart rate 131 beats/minute in atrial fibrillation, MAP 62 mm Hg (by arterial blood pressure catheter), respiratory rate 22 breaths/minute, and temperature 100.8°F (38.2°C). An arterial blood gas show lactate 5.2 mmol/L. An arterial pulse pressure waveform analysis monitor shows pulse pressure variation (PPV) 18%. The patient has a central venous catheter in his right femoral vein. Which next step is best?

A. Give 1 L of lactated Ringer's solution.
B. Do a passive leg raising (PLR) test.
C. Measure CVP.
D. Send a blood gas for venous oxygen saturation.

6. A 19-year-old man is admitted to the medical ICU for hypotension after being stung by a bee. He was given intramuscular epinephrine by emergency medical services and transferred to the emergency department (ED). On arrival at the ED, his blood pressure was 78/42 mm Hg; he was given 1 L of 0.9% sodium chloride, diphenhydramine, famotidine, and methylprednisolone. The patient remained hypotensive but responded to an additional 2 L of 0.9% sodium chloride. He was transferred to the medical ICU for further treatment. On arrival in the medical ICU, his MAP is 62 mm Hg. A right internal jugular central venous catheter is placed, which shows CVP 3 mm Hg, Scvo$_2$ 61%, venous lactate concentration 4.4 mmol/L, and hemoglobin (Hgb) 9.6 g/dL. Together with further fluid resuscitation, which agent would be best to initiate or administer?

A. Packed red blood cells (PRBCs).
B. Dobutamine.
C. Milrinone.
D. Norepinephrine.

7. A 56-year-old man (weight 66 kg) presents to the ED with presumed community-acquired pneumonia. Blood cultures are obtained, and the patient is given ceftriaxone 1 g and levofloxacin 750 mg. His initial blood pressure is 83/47 mm Hg with a lactate concentration of 6.2 mmol/L, and he is given 1.5 L of 0.9% sodium chloride over 1 hour. Subsequently, his blood pressure is 92/54 mm Hg with a lactate concentration of 4.6 mmol/L and urinary output of 30 mL/hour. A central venous catheter placed in his right internal jugular vein shows a CVP of 6 mm Hg, and a venous blood gas reading obtained from the central venous catheter shows an Scvo$_2$ of 63%, Hgb 9.2 g/dL, and hematocrit (Hct) 28%. Which would be the best therapy for this patient right now?

A. 0.9% sodium chloride.
B. 5% albumin.
C. Phenylephrine.
D. PRBCs.

8. A 68-year-old woman (weight 88 kg) presents to the ED with a urinary tract infection. Her medical history is significant for paroxysmal atrial fibrillation. The patient's vital signs in the ED are as follows: blood pressure 83/47 mm Hg, heart rate 118 beats/minute in atrial fibrillation, respiratory rate 24 breaths/minute, and temperature 102°F (38.9°C). Her laboratory values of interest in the ED include white blood cell count (WBC) 19.6 × 10^3 cells/mm^3, Hgb 9.3 g/dL, albumin 2.4 g/dL, lactate 4.9 mmol/L, and SCr 1.2 mg/dL. Blood and urinary cultures are obtained, and she receives levofloxacin 750 mg and 3 L of 0.9% sodium chloride. Thirty minutes after completing the 0.9% sodium chloride infusion, her blood pressure is 92/49 mm Hg with a lactate concentration of 4.6 mmol/L and urinary output of 30 mL/hour. Which would be the best therapy for this patient right now?

   A. Norepinephrine.
   B. Vasopressin.
   C. Phenylephrine.
   D. Dopamine.

9. A 34-year-old man is admitted to the surgical ICU with septic shock associated with necrotizing soft tissue infection of the right leg. He received 100% oxygen by high-flow mask; adequate broad-spectrum antibiotics with vancomycin, piperacillin/tazobactam, and clindamycin; and quantitative resuscitation. The patient has been resuscitated for the past 4 hours with 5 L of normal saline and currently is hemodynamically unstable on norepinephrine 14 mcg/minute with a corresponding blood pressure of 92/45 mm Hg and heart rate of 132 beats/minute in sinus rhythm. His CVP is 12 mm Hg, $Scvo_2$ 72%, urinary output 0.3 mL/kg/hour, and lactate 7.4 mmol/L. Which would be best to initiate for this patient?

   A. 0.9% sodium chloride.
   B. Vasopressin.
   C. Phenylephrine.
   D. Epinephrine.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
   a. Task A: 1, 2, 4
2. Domain 2: Therapeutics and Patient Management
   a. Task A: 1, 2, 4, 8
   b. Task B: 2, 15
   c. Task C: 1, 3

I. INTRODUCTION

A. Shock
1. Shock is a heterogeneous group of syndromes best defined as "acute circulatory failure." This arises when the tissues receive an insufficient supply of oxygen to be able to perform vital metabolic functions.
2. Shock is often categorized into four distinct etiology mechanisms: (1) hypovolemic, (2) obstructive, (3) distributive and vasodilatory, and (4) cardiogenic. In some clinical scenarios, multiple shock syndromes can occur simultaneously.
3. The diagnosis of shock typically includes the interpretation of three variables: hemodynamic assessment, clinical presentation, and biochemical signs.
4. In many cases, shock is first identified by the presence of hypotension. However, the blood pressure limits used to define shock are arbitrary and may not be patient-specific (e.g., a patient with hypertension before critical illness).
   a. In shock states, the value typically used to describe hypotension is a systolic blood pressure (SBP) less than 90 mm Hg or a mean arterial pressure (MAP) less than 70 mm Hg.
   b. These values may vary within a range to permit autoregulation, allowing acceptable perfusion in the setting of acute hypotension.
5. Clinical presentation of shock may be subtle and can manifest in many different ways. Usually, shock is identified through an assessment of mentation, skin, and kidney function.
   a. Assessment of mentation should include a careful examination for signs of confusion and obtundation. These signs should be compared with those in the patient's preexisting status. This may be challenging in a patient who is a poor historian or in those with a diminished baseline status.
   b. Evidence of an existing shock syndrome can manifest with decreased capillary refill and cold, clammy skin.
   c. Altered kidney function in the setting of shock primarily presents with reduced urinary output (e.g., less than 0.5 mL/kg/hour). Laboratory values such as serum creatinine (SCr) often lag behind the immediate observation of urine volume and quality.
6. Biochemical assessment of patients with shock typically reveals hyperlactatemia (greater than 2 mmol/L) or reduced venous oxygen saturation (Svo_2) (less than 70%), indicating abnormal cellular oxygen metabolism.

B. Physiology
1. Hemodynamic parameters can be either directly measured from a monitoring device or calculated according to direct measurements (see Table 1).

Table 1. Hemodynamic and Oxygen Transport Values

Value	Equation (as applicable)	Normal Value
Systolic blood pressure (SBP)		90–140 mm Hg
Diastolic blood pressure (DBP)		60–90 mm Hg
Mean arterial blood pressure (MAP)[a]	[SBP + (2 × DBP)]/3	70–100 mm Hg
Heart rate (HR)		60–80 beats/min
Cardiac output (CO)[b]	HR•SV	4–7 L/min
Cardiac index (CI)	CO/BSA	2.5–4.2 L/min/m^2
Stroke volume (SV)	CO/HR	60–130 mL/beat
Pulmonary artery systolic pressure (PASP)		20–30 mm Hg

Table 1. Hemodynamic and Oxygen Transport Values *(continued)*

Value	Equation (as applicable)	Normal Value
Pulmonary artery diastolic pressure (PADP)		8–12 mm Hg
Mean pulmonary artery pressure (mPAP)	[PASP + (2 × PADP)]/3	12–15 mm Hg
Pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusion pressure (PAOP)		5–12 mm Hg
Central venous pressure (CVP) or right atrial pressure (RAP)		2–6 mm Hg
Pulmonary vascular resistance (PVR)[c]	80 × [(mPAP − PCWP)/CO] (divide by 80 for Wood units)	20–120 dynes•s•cm-5 (< 2 Wood units)
Systemic vascular resistance (SVR)[c]	80 × [(MAP − CVP)/CO]	800–1200 dynes•s•cm-5
Oxygen delivery (Do_2)[d]	10 × CO (L/min) × Cao_2	520–570 mL/min/m^2
Arterial oxygen content (Cao_2)[d]	(1.34 × Hgb × Sao_2) + (0.003 × Pao_2)	20 mL/dL
Venous oxygen content (Cvo_2)[d]	(1.34 × Hgb × Svo_2) + (0.003 × Pvo_2)	15 mL/dL
Resting oxygen consumption (Vo_2)[d]	10 × CO (L/min) × (Cao_2 − Cvo_2)	110–160 mL/min/m^2
Oxygen extraction ratio (O2ER)	Vo_2/Do_2 × 100	20%–30%

[a] May be directly measured or calculated.

[b] May be measured using several mechanisms, including thermodilution with a pulmonary artery catheter. May also be calculated using the Fick equation (see later in the chapter).

[c] May also be expressed as an indexed value calculated by dividing the value by body surface area. BSA = body surface area in square meters.

[d] All are components of the Fick principle for cardiac output measurement.

BSA = body surface area; Cao_2 = arterial oxygen content; CI = cardiac index; CO = cardiac output; Cvo_2 = venous oxygen content; CVP = central venous pressure; DBP = diastolic blood pressure; Do_2 = oxygen delivery; Hgb = hemoglobin; HR = heart rate; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; O2ER = oxygen extraction ratio; PADP = pulmonary artery diastolic pressure; Pao_2 = arterial partial pressure of oxygen or arterial oxygen tension; PAOP = pulmonary arterial occlusion pressure; PASP = pulmonary arterial systolic pressure; PCWP = pulmonary capillary wedge pressure; Pvo_2 = venous partial pressure of oxygen or venous oxygen tension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; Sao_2 = arterial oxygen saturation; SBP = systolic blood pressure; SV = stroke volume; Svo_2 = venous oxygen saturation; Vo_2 = resting oxygen consumption.

Modified with permission from: Wittbrodt ET, Tietz KJ. Shock syndromes. In: Carter BL, Lake KD, Raebel MA, et al., eds. Pharmacotherapy Self-Assessment Program, 3rd ed. Module 2: Critical Care. Kansas City, MO: American College of Clinical Pharmacy, 1998:87-127.

2. MAP is the driving pressure for peripheral blood flow (and end-organ perfusion). Sufficient arterial pressure allows redistribution of cardiac output (CO) to vital organs.
3. Blood pressure is the product of CO and systemic vascular resistance (SVR).
4. CO is the product of heart rate and stroke volume (SV).
5. SV is determined by many factors, but predominantly preload, intrinsic contractility, and afterload.
   a. Preload refers to ventricular end-diastolic volume and is proportionally related to SV (i.e., when preload increases, the SV increases) by the Frank-Starling mechanism (though the magnitude of this relationship is reduced beyond a point of ventricular increasing end-diastolic volume).
   b. Intrinsic contractility is the ability of the myocardium to contract and may be reduced by several factors, including myocardial ischemia, cardiomyopathy, and sepsis.
   c. Afterload is the force the ventricle must overcome to eject its volume and is inversely related to SV (i.e., when afterload increases, the SV decreases). Left ventricular (LV) afterload is predominantly influenced by aortic pressure, whereas right ventricular (RV) afterload is predominantly influenced by pulmonary artery pressure.

6. SVR (also termed *total peripheral resistance*) is the resistance to flow that must be overcome by the left ventricle.
   a. SVR is the major determinant of LV afterload.
   b. Systemic vasoconstriction increases SVR, whereas vasodilation decreases SVR.
   c. Skin temperature may be used as an approximation (surrogate) of SVR, in which warm skin temperature suggests decreased SVR (vasodilation) and cold skin temperature suggests increased SVR (vasoconstriction).
7. The right ventricle better tolerates increases in ventricular volume (preload) than increases in afterload. Contrarily, the left ventricle better tolerates increases in afterload than increases in ventricular volume.
8. Coronary artery perfusion occurs primarily in diastole. Aortic diastolic pressure must be sufficient to ensure perfusion of the coronary arteries.

C. Oxygen Delivery (Do_2) and Oxygen Consumption (Vo_2)
1. The circulatory system delivers oxygen and vital nutrients to the tissue beds for homeostasis and end-organ function.
2. Oxygen is inspired and delivered to the alveoli, where it binds reversibly to hemoglobin.
3. Oxygen bound to hemoglobin is then transported by CO to the tissues. The rate of Do_2 is the product of the CO and the arterial oxygen content (Cao_2), as described in Table 1. Metabolic function of tissue beds requires consistent Do_2.
4. At the tissues, oxygen dissociates from hemoglobin and is taken up by the mitochondria through systemic capillaries for aerobic metabolism. Oxygen uptake or Vo_2 is the rate at which oxygen transfers from systemic capillaries into the tissues and is the byproduct of CO, Cao_2, and venous oxygen content (Cvo_2).
5. The Fick equation states that $CO = Vo_2/(Cao_2 - Cvo_2)$.
6. The oxygen extraction ratio (O_2ER), or the ratio of Vo_2/Do_2, is 20%–30% at resting state, meaning that about 25% of the oxygen delivered to the capillaries is taken up by the tissues. The O_2ER is relatively stable and can accommodate temporary fluctuations in Do_2 or Vo_2. Sustained Do_2/Vo_2 mismatches contribute to tissue hypoxia and deranged metabolic function.
7. Treatment of shock syndromes should be rapid to minimize permanent tissue and organ damage.
8. In the early stages of a shock state, blood pressure is preserved through stimulation of the sympathetic system, release of endogenous vasopressin, and vasoconstriction through the formation of angiotensin II. The synergy of these actions preserves blood flow and Do_2 to vital organs.
9. Blood flow is prioritized to maximize Do_2 to the heart and brain. Consequently, blood flow to extravital organs (e.g., skin, gut, kidneys) is redirected.
10. When the endogenous response to shock is insufficient either in magnitude or duration, blood pressure decreases, and overt shock develops.

II. MONITORING TECHNIQUES

A. Hemodynamic Monitoring Devices
1. Hemodynamic variables may be obtained through noninvasive or invasive monitoring devices (Table 2).
2. In patients with shock in whom the clinical examination does not lead to a clear diagnosis, further hemodynamic assessment is recommended.

3. In general, less invasive devices are desired, but they often have limited accuracy in estimating hemodynamic parameters compared with invasive devices.
4. When further hemodynamic assessment is indicated, echocardiography is the preferred modality to initially evaluate the type of shock as opposed to more invasive approaches.
5. Some ICU monitors can display additional hemodynamic parameters (e.g., automated PPV from an arterial catheter) without additional equipment or devices.
6. Bioimpedance uses electrodes on the skin or an endotracheal tube to estimate the CO through mathematical modeling of the impedance by the body to electrical current flow induced by cyclic changes in blood flow during the cardiac cycle. Bioreactance improves on bioimpedance models by analyzing the variations in the whole frequency spectra of the oscillating current instead of only variations in amplitude changes. This increases the signal-to-noise ratio and improves device performance.

Table 2. Hemodynamic Monitoring Devices

Device or Category	Obtainable Parameters	Advantages	Limitations
Noninvasive BP monitoring[a]	SBP, DBP, MAP	• Noninvasive • Bedside practitioner familiarity	• Limited accuracy in shock • Does not provide continuous monitoring • Less sensitive in predicting end-organ dysfunction
Arterial BP catheter	SBP, DBP, MAP	• More accurate BP measurement in shock than noninvasive methods • Ready access for arterial blood gas sampling • Continuous monitoring	• Invasive • Inaccurate damping influences SBP and DBP measurements (MAP still accurate) • Catheter-related infection • Brachial site lacks collateral circulation (may result in decreased distal arterial perfusion)
Central venous catheter (CVC)	CVP/RAP, $Scvo_2$	• Easier and safer to insert than a PAC • $Scvo_2$ may be available as a continuous measurement • Access for administration of highly osmotic and caustic agents	• CVP/RAP not a true estimate of LV end-diastolic pressure • CVP/RAP does not accurately predict fluid responsiveness • $Scvo_2$ not equivalent to Svo_2 (see later in the chapter)

Table 2. Hemodynamic Monitoring Devices *(continued)*

Device or Category	Obtainable Parameters	Advantages	Limitations
Pulmonary artery catheter (PAC)	Measured: PASP, PADP, mPAP, CVP/RAP, PCWP/PAOP, CO, and CI by thermodilution or continuous measurement (copper filament adapted catheter), Svo_2 Calculated: PVR, SVR, CO, and CI by Fick equation, SV	• Only method available to directly measure pulmonary artery pressures • Direct measurement of CO and Svo_2 (may be available as continuous variables)	• Outcomes data supporting superiority to CVC lacking • May cause arrhythmias • Assumes right heart function approximates left heart function (usually, but not always, true) • Fick CO calculation typically uses an estimated value for Vo_2, which may be falsely low in a patient with septic shock and underestimate CO • Valvular abnormalities may make values inaccurate (particularly mitral stenosis, mitral regurgitation, tricuspid regurgitation, or aortic regurgitation) • Correct catheter tip location (lung zone 3) needed for accurate readings
Echocardiography	Cardiac chamber size and function, pericardial appearance (and presence of fluid), IVC collapsibility/distensibility, ejection fraction, RVSP (an estimate of PASP), LVOT VTI (to calculate CO/CI)	• Noninvasive (transthoracic) • Visualization of ventricular function instead of presumed function based on CO • IVC collapsibility can predict fluid responsiveness	• Subjectivity of user assessment • Not done continuously; therefore, cannot detect acute changes or must be repeated when the patient's status changes • May have limited visibility/windows depending on patient body habitus or positioning
Esophageal Doppler (ODM II, CardioQ, HemoSonic 100)	CO, CI, SV, flow time	• Ease of use • May be used to determine fluid responsiveness	• Assumptions used by the device may not be valid in the setting of hemodynamic instability (fixed partition of blood flow to cephalic vessels and descending aorta, constant aortic cross-sectional area) • Accuracy depends on position (need for frequent repositioning)

Table 2. Hemodynamic Monitoring Devices *(continued)*

Device or Category	Obtainable Parameters	Advantages	Limitations
Arterial pulse pressure waveform analysis (FloTrac/Vigileo, PiCCOplus, PulsioFlex, LiDCO plus, PRAM-MostCare, Nexfin)	CO and CI, SV, SVR (calculated), SVV, PPV	• Continuous measurement of values • Allows for assessment of SVV and PPV, which are dynamic markers of fluid responsiveness in mechanically ventilated patients (see later in the chapter) • Minimally invasive (Nexfin is noninvasive)	• Accuracy relies on optimal arterial waveform from arterial catheter • Inaccurate in patients with mitral or aortic valve disease or when used concomitantly with an intra-aortic balloon pump • Arrhythmias reduce the accuracy of reported CO and CI (though this may be accounted for by internal software with some devices) • Accuracy may be limited during rapid changes in vascular resistance • Some devices require a CVC in addition to an arterial pressure catheter • Interpretation of SVV and PPV is limited by the need for positive pressure ventilation, no spontaneous breaths being triggered by the patient, and relatively large tidal volumes • SVV and PPV are not accurate predictors of fluid responsiveness in the setting of arrhythmias
Bioimpedance/ bioreactance (NICOM, BioZ, ECOM)	Continuous CO and CI, SV, SVR, SVV	• Noninvasive • NICOM CO correlates well with CO values from thermodilution and pulse pressure waveform analysis	• Conflicting validation results with BioZ and ECOM, particularly in patients with septic shock • ECOM requires endotracheal intubation

[a] Includes manual sphygmomanometry and automated oscillometric (cuff) techniques.

BP = blood pressure; CVC = central venous catheter; CVP = cental venous pressure; IVC = inferior vena cava; LV = left ventricular; LVOT VTI = left ventricular outflow tract velocity time integral; mPAP = mean pulmonary artery pressure; PAC = pulmonary artery catheter; PADP = pulmonary artery diastolic pressure; PAOP = pulmonary artery occlusion pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure PPV = pulse pressure variation; RAP = right atrial pressure; RVSP = right ventricular systolic pressure; Scvo$_2$ = central venous oxygen saturation; SVR = systemic vascular resistance; SVV = stroke volume variation.

Information from: Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. Crit Care 2011;15:214.

B. Markers of Perfusion
  1. Global perfusion
    a. End-organ function (altered mental status, low urinary output, and mottled skin, as noted earlier)
    b. Elevated blood lactate concentration (above 2 mmol/L)
      i. Lactate is produced from pyruvate by lactate dehydrogenase as an end product of glycolysis under anaerobic conditions.
      ii. Most lactate is cleared by the liver by conversion back to pyruvate in the Cori cycle, with a small amount cleared by the kidneys. Severe liver dysfunction may impair lactate clearance and accentuate lactate concentration elevations in shock.

    iii. Elevated lactate concentrations may be the result of increased production, decreased clearance, or both.
        (a) Type A lactic acidosis occurs in the setting of Do_2/Vo_2 mismatch (oxygen demand exceeds supply).
        (b) Type B lactic acidosis is not related to tissue hypoxia and typically occurs in the setting of impaired lactate clearance or medication-related causes (e.g., metformin, epinephrine, linezolid, or toxic alcohols).
    iv. Arterial and venous lactate concentrations are slightly different in value but may be used interchangeably. When trending lactate values over time, consistent methods of collection should be used.

c. Venous oximetry ($Scvo_2$ and Svo_2)
    i. Central venous oxygen saturation ($Scvo_2$) and mixed venous oxygen saturation (Svo_2) are the oxyhemoglobin saturations of venous blood obtained from a central vein and the pulmonary artery, respectively, and are expressed as a percentage.
    ii. $Scvo_2$ is obtained from a central venous catheter (i.e., subclavian or internal jugular access) where the catheter tip terminates in the superior vena cava. As such, $Scvo_2$ is more reflective of oxygen extraction in the brain and upper body than of systemic oxygen extraction. Of importance, the oxyhemoglobin saturation of blood obtained from a central venous catheter terminating in the IVC (i.e., femoral access) cannot be used interchangeably with the $Scvo_2$ obtained from a central venous catheter terminating in the superior vena cava and should not be used as a marker of perfusion.
    iii. Svo_2 better represents systemic oxygen extraction because it represents the mixing of venous blood from the superior vena cava, inferior vena cava (IVC), and coronary sinus.
    iv. In normal physiology, $Scvo_2$ is about 2%–3% lower than Svo_2 because the upper body and the brain extract more oxygen than the lower body.
    v. In the setting of shock, $Scvo_2$ exceeds Svo_2 by about 5%–8% because of increased mesenteric and renal oxygen extraction with a similar cerebral extraction ratio.
    vi. The difference between $Scvo_2$ and Svo_2 decreases in low CO states.
    vii. Although $Scvo_2$ and Svo_2 are not equivalent, they have a good (though not perfect) correlation, and $Scvo_2$ may be a reasonable approximation of Svo_2, given its requirement for a PAC for accurate measurement.
    viii. A decreased $Scvo_2$ or Svo_2 is a sign that tissue oxygen demands are not completely met by Do_2 (more discussion on this topic later in this chapter).
    ix. Rearrangement of the Fick equation shows that a decrease in Svo_2 indicates a decrease in CO, whereas an increase in Svo_2 indicates an increase in CO.
    x. In general, Svo_2 values above 70% are considered adequate, whereas Svo_2 values less than 40% are considered critically low and approach the critical O_2ER where anaerobic metabolism will occur and lactate concentrations will increase. Svo_2 values of 50%–70% by themselves do not lead to firm conclusions about the O_2ER and must be interpreted in the context of other markers of tissue perfusion (e.g., lactate concentrations).
    xi. Svo_2 values above 80% likely indicate poor tissue oxygen extraction capacity.
        (a) This may occur because of the heterogeneity of microvascular and macrovascular blood flow (i.e., microcirculatory dysfunction), peripheral shunting of oxygen past the tissues, or impaired mitochondrial oxygen use.
        (b) Patients with septic shock and venous hyperoxia ($Scvo_2$ greater than 89%) within the first 6 hours of their treatment had a higher mortality than those with normoxia ($Scvo_2$ 71%–89%).

2. Regional tissue perfusion
   a. Microcirculatory blood flow
      i. The microcirculation consists of arterioles, capillaries, and venules and is where oxygen release to the tissues occurs.
      ii. Traditional resuscitation strategies have focused on hemodynamic and Do_2 end points (the “macrocirculation”), but the microcirculation plays a key role in tissue oxygenation in shock (particularly in septic shock) and has historically been overlooked.
      iii. Of importance, microcirculatory blood flow and Do_2 cannot be predicted by global (macrocirculatory) hemodynamics.
      iv. Microcirculatory blood flow can be visualized with orthogonal polarization spectral imaging or sidestream darkfield imaging. These devices use green light to illuminate tissue, which is absorbed by the hemoglobin of red blood cells. This allows the microcirculation to be visualized because of its red blood cell content.
      v. The sublingual microcirculation has been studied most often because of its accessibility.
      vi. Studies have shown that the microcirculation is often altered in patients with sepsis, persistent microvascular alterations are associated with multisystem organ failure and death, alterations are more severe in non-survivors than in survivors, and improvements in microcirculatory blood flow correspond with improved patient outcomes.
      vii. Decreased vascular density, decreased capillary perfusion, and a decreased percentage of perfused small vessels are the most common microcirculatory alterations. The proportion of perfused small vessels seems to be the strongest microcirculatory blood flow predictor of patient outcomes. In one study of patients with sepsis and septic shock, this was a stronger predictor of mortality than global hemodynamic markers.
      viii. Heterogeneity has been observed in microcirculatory blood flow in the same tissue bed (with as little as a few millimeters between observations) and between different tissue beds.
      ix. Evaluation of the microcirculation is not commonly used in clinical practice because it requires extensive user experience to obtain proper measurements and time to analyze the results. However, this is an attractive marker of tissue perfusion that, with technical advances, may be used more often in the future.
   b. Elevated lactate concentrations may also indicate regional tissue hypoperfusion (e.g., mesenteric ischemia or critical limb ischemia).
   c. Capillary refill time (measured as the time it takes to recolor a fingertip after pressure application) can also be used as a marker of tissue hypoperfusion. Capillary refill times greater than 3 seconds are often considered abnormal and an indicator of poor tissue perfusion.
   d. Other measures of regional tissue perfusion include gastric tonometry to indirectly assess gastric mucosal perfusion and near-infrared spectroscopy, a noninvasive method of measuring tissue oxygen saturation (Sto_2) in a skeletal muscle.

Patient Case

1. A 77-year-old man presents to the ED with light-headedness and fatigue. He reports increasing melena during the past 24 hours. His medical history is significant for hypertension, asthma, and gastroesophageal reflux disease. Vital signs in the ED are as follows: blood pressure 88/54 mm Hg, heart rate 124 beats/minute, respiratory rate 18 breaths/minute, and temperature 102.2°F (39°C). While interviewing the patient, you note that he appears lethargic and confused. His serum chemistry panel shows the following: Na 138 mEq/L, K 3.8 mEq/L, Cl 105 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 25 mg/dL, SCr 1.1 mg/dL, and glucose 78 mg/dL. Results of the complete blood cell count (CBC) are as follows: WBC 10.2×10^3 cells/mm^3, Hgb 6.6 g/dL, Hct 19.2%, and platelet count (Plt) 180,000/mm^3. Which is most likely contributing to this patient's compromised Do_2 to the end organs?
   A. Medical history of hypertension.
   B. Reduced Hgb.
   C. Tachycardia.
   D. Leukocytosis.

III. DIFFERENTIATION OF SHOCK STATES

A. Determining which shock state is present is typically based on assessments of preload (CVP or pulmonary capillary wedge pressure [PCWP]), CO ($Scvo_2$ or Svo_2 may serve as a surrogate), and afterload (SVR) (see Table 3).

B. Values to describe this hemodynamic profile have historically been obtained from a pulmonary artery catheter (PAC), but bedside echocardiography is now recommended as the preferred modality to initially evaluate the type of shock.

Table 3. Hemodynamic Profiles of Shock States

Shock State	CVP	PCWP	CO	SVR
Hypovolemic	↓[a]	↓[a]	↓	↑
Cardiogenic	↑	↑	↓[a]	↑
Obstructive				
Impaired diastolic filling (e.g., cardiac tamponade)	↑	↑	↓[a]	↑
Impaired systolic contraction (e.g., massive PE)	↑	↓ or ↔	↓[a]	↑
Vasodilatory/distributive				
Pre-resuscitation	↓	↓	↓	↓[a]
Post-resuscitation	↑	↑	↑	↓[a]

[a] Pathophysiologic hallmark of shock state.

PE = pulmonary embolism; SVR = systemic vascular resistance.

Information from: Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013;369:1726-34; Dellinger RP. Cardiovascular management of septic shock. Crit Care Med 2003;31:946-55; Weil MH, Shubin H. Proposed reclassification of shock states with special reference to distributive defects. Adv Exp Med Biol 1971;23:13-23.

C. The hemodynamic profiles in Table 3 occur when the stated shock state occurs independently, which often does not occur because patients often have features of combined shock states.

D. A patient's history of present illness can help differentiate between shock states. For example, a patient presenting after motor vehicle collision likely has hypovolemic shock, whereas a patient presenting after bee sting likely has vasodilatory/distributive shock (immune-mediated [anaphylactic] subtype).

IV. RESUSCITATION PARAMETERS AND END POINTS

A. The approach to treating a patient with circulatory shock can be divided into four phases, each having different (but sometimes overlapping) treatment goals and therapeutic strategies. Although the rest of this chapter focuses on the first 2 phases, understanding the phase of a patient's circulatory shock is essential for establishing treatment goals and subsequent therapeutic approaches.

1. Salvage: The first phase focuses on salvage, in which efforts should be directed to achieving the minimum perfusion pressure and CO needed to maintain the patient's survival. Treating the underlying cause of the patient's shock, which consists of lifesaving measures, should be done at this time. Examples of these measures include antimicrobials for sepsis, revascularization for acute myocardial infarction, and surgical hemostasis for trauma.
2. Optimization: Optimization is the second phase with the goal to ensure adequate Do_2.
3. Stabalization: In the third phase, patient stabilization is targeted with the goal of preventing or minimizing end-organ dysfunction.
4. De-escalation: The fourth phase is de-escalation, in which the goals of therapy include vasoactive medications weaning (or cessation), fluid elimination (e.g., diuresis or ultrafiltration), and antimicrobial de-escalation as dictated by microbiology cultures, local antibiogram, and patient clinical picture.

B. Blood Pressure

1. As noted earlier, blood pressure is the driving pressure for peripheral blood flow. As such, an adequate blood pressure is vital to ensure end-organ perfusion.
2. MAP is the true driving pressure for peripheral blood flow and end-organ perfusion and is preferred to SBP or diastolic blood pressure as a therapeutic target.
3. The perfusion pressure of any organ can be calculated by subtracting the pressure within the organ or anatomic space from the MAP (e.g., cerebral perfusion pressure = MAP − intracranial pressure).
4. The target blood pressure for a patient in shock is usually a MAP greater than 65 mm Hg or an SBP greater than 90 mm Hg, but this must be individualized according to other clinical/biochemical markers of perfusion.
5. MAP is an insensitive resuscitation parameter (e.g., blood pressure may be at goal when CO is inadequate), because of this, additional resuscitation parameters should be used to ensure the optimization of all hemodynamic components that may influence end-organ perfusion and Do_2.
6. These additional resuscitation goals typically include ensuring (1) adequate end-organ perfusion, (2) lack of fluid responsiveness, and (3) adequate Do_2.

C. Adequate End-Organ Perfusion

1. Each organ has a critical perfusion pressure that must be exceeded to maintain adequate perfusion. This critical perfusion pressure is organ- and patient-specific because of adaptation for chronic conditions.
2. As the MAP decreases, the perfusion pressure of the organ decreases, and subsequently, organ function decreases.
3. Adequate organ perfusion is best assessed clinically on a per-patient basis.

4. General goals of therapy include resolution of altered mental status and adequate urinary output (above 0.5 mL/kg of body weight per hour). However, these goals may be challenging to assess in patients who are given medications that mask the ability to assess the organ function (e.g., sedatives) or in patients with chronic organ dysfunction (e.g., end-stage renal disease).

D. Fluid Responsiveness
1. Intravenous fluids are given to increase preload and subsequently increase SV, increase CO, and increase Do_2.
2. Fluids should be given only if there is inadequate effective organ perfusion caused by inadequate CO (presumably because of inadequate SV) and if the patient is fluid responsive.
    a. Fluid responsiveness is defined as at least a 10%–15% increase in CO after fluid administration.
    b. This is best assessed by giving a fluid challenge and evaluating the response.
    c. A change in blood pressure is not a reliable indicator of CO response to a fluid challenge; an assessment of CO (or SV) change should be used instead.
    d. In one systematic review, only 57% of hemodynamically unstable patients were fluid responsive.
3. Patients given additional fluid when they are no longer fluid responsive will not experience the beneficial effects of fluid (increased CO)—only the harmful effects (e.g., pulmonary edema). Although an argument could be made to determine fluid responsiveness in each patient, it is most critical in patients for whom harmful fluid effects cannot be tolerated (e.g., those with refractory hypoxemia in the setting of shock).
4. Fluid responsiveness may be predicted by static or dynamic markers.
    a. Static markers of fluid responsiveness include the cardiac filling pressures CVP and PCWP.
    b. Dynamic markers of fluid responsiveness include stroke volume variation (SVV), systolic pressure variation, pulse pressure variation (PPV), and IVC variation.
5. Although CVP and PCWP may help differentiate shock states and may help to provide an understanding of static intravascular volume status, they are not reliable predictors of fluid responsiveness.
    a. In one study of patients with sepsis and septic shock, a CVP less than 8 mm Hg and a PCWP less than 12 mm Hg had fluid responsiveness positive predictive values of 47% and 54%, respectively.
    b. Systematic reviews and meta-analyses suggest that CVP should not be used as a resuscitation parameter.
6. Fluid responsiveness is better predicted by dynamic markers of fluid responsiveness than by static markers of volume status or fluid responsiveness.
    a. The area under the receiver operating characteristic curve (AUC ROC), with the optimal area of 1, for predicting fluid responsiveness is as follows: PPV 0.94 (95% confidence interval [CI], 0.93–0.95), systolic pressure variation 0.86 (0.82–0.90), and SVV 0.84 (0.78–0.88). In contrast, the AUC ROC for predicting fluid responsiveness for CVP is 0.55 (0.48–0.62).
    b. Because they can be obtained from monitoring devices (Table 2), PPV and SVV are more commonly used in practice than is systolic pressure variation.
7. The dynamic markers, PPV, SVV, and IVC collapsibility, are based on heart-lung interactions in mechanically ventilated patients.
    a. In mechanically ventilated patients, a controlled positive pressure breath increases pleural pressure. This increase in intrathoracic pressure leads to a decrease in venous return, decreased RV preload, and decreased RV SV. LV preload is subsequently decreased, which may lead to a decrease in LV SV.
    b. Patients who are preload (fluid) responsive (on the steep rather than the flat portion of the Frank-Starling curve) will have relatively large changes in LV SV with positive pressure breaths. This leads to variation in the LV SV between periods with and without positive pressure breaths.
    c. Some ICU monitors can display automated PPV from an arterial catheter without additional monitoring equipment or devices.

   d. The specific values of PPV and SVV used to predict fluid responsiveness vary by study, specific conditions (e.g., use of vasopressors), and assessment method or device. In a systematic review, thresholds to predict fluid responsiveness were PPV greater than 12.5% and SVV greater than 11.6%.
   e. IVC variation (also termed *IVC collapsibility* or *IVC distensibility*) uses echocardiography to visualize the diameter of the IVC during positive pressure ventilation. With a positive pressure breath from mechanical ventilation, venous return is impaired, and the diameter of the IVC increases (IVC distensibility). The opposite change in IVC diameter occurs in patients breathing spontaneously (IVC collapsibility). The change in IVC diameter during inspiration is higher in patients who are fluid responsive than in those who are not fluid responsive.
      i. In one study, the AUC ROC for predicting fluid responsiveness for IVC distensibility was 0.84 (95% confidence interval [CI], 0.63–1.0), and the best cutoff was 16% (sensitivity 67%, specificity 100%).
      ii. In a larger, multicenter study of mechanically ventilated patients with varied causes of circulatory shock, IVC distensibility had an AUC ROC for predicting fluid responsiveness of 0.64 for a threshold of 8% (sensitivity 55%, specificity 70%). In the patient subset with all assessed dynamic markers of fluid responsiveness available, the AUC ROC for predicting fluid responsiveness was significantly higher for respiratory variations in superior vena cava diameter (0.74, threshold of 21% or greater) than PPV (0.66, threshold of 11% or greater, p=0.01) and IVC distensibility (0.65, threshold of 13% or greater, p=0.02). Of note, superior vena cava diameter changes must be assessed by transesophageal echocardiography, which is not commonly performed for this purpose in the United States. IVC variation may be assessed by transesophageal or transthoracic echocardiography.

8. The passive leg raise (PLR) test measures the hemodynamic effects of a positional change in the patient's legs. Changing the position of the patient's bed such that the patient's legs are lifted to a 45-degree angle with the patient's head placed horizontally leads to a transfer of blood from the abdominal compartment and lower extremities to the intrathoracic compartment.
   a. This increase in venous return may subsequently increase SV and CO if the patient is preload responsive.
   b. An increase in CO by 10%–15% after PLR is considered a positive test.
   c. The benefit of the PLR test is that it can be used in spontaneously breathing or nonintubated patients. In addition, it does not require the administration of fluid (which may be harmful if the patient is not fluid responsive) and can easily be reversed by returning patients to their previous position.
   d. A caveat to use of the PLR test is that a method of evaluating CO is required to determine response (or lack thereof). A change in blood pressure is not an adequate surrogate marker for CO, as noted earlier. The CO measurement may be obtained from an arterial pulse pressure waveform analysis monitor (minimally invasive approach) or from a bioimpedance device, bioreactance device, or echocardiographic LVOT VTI (noninvasive approach).
9. Several caveats exist for using dynamic markers of fluid responsiveness.
   a. PPV and SVV assume the following: sinus cardiac rhythm, the absence of significant valvular dysfunction, intubation and mechanical ventilation without spontaneous breaths, and tidal volume of 8 mL/kg or more of predicted body weight. Values for PPV and SVV above the noted thresholds do not reliably predict fluid responsiveness in the setting of arrhythmias (e.g., atrial fibrillation). If these assumptions are not fulfilled, PPV and SVV are not reliable in predicting fluid responsiveness.
   b. IVC distensibility also requires intubation and mechanical ventilation without spontaneous breaths and is not conducive to continuous monitoring.
   c. The real-time response of CO (or lack thereof) with PLR must be assessed using a CO monitoring device. In addition, intra-abdominal hypertension reduces the ability of PLR to detect fluid responsiveness.

10. The best dynamic marker of fluid responsiveness to use in practice is unclear.
    a. In the previously mentioned study, the AUC ROC for predicting fluid responsiveness was higher for PPV than for SVV.
    b. In one study of postoperative patients, IVC distensibility was not noninferior to PPV (noninferiority p=0.28), considering a noninferiority margin of 15%.
    c. However, obtaining PPV from echocardiography leads to a lower AUC ROC for predicting fluid responsiveness (0.66–0.68) than does obtaining PPV from other methods (AUC ROC 0.94).
    d. In patients in whom transesophageal echocardiography is performed, superior vena cava diameter changes appear to be superior to IVC distensibility and PPV.
11. Despite the superiority of dynamic markers to static markers in predicting fluid responsiveness, incorporating dynamic markers into a resuscitation strategy that improves patient outcomes in the ICU is still lacking.
    a. In a randomized controlled trial of patients with septic shock and/or acute respiratory distress syndrome that randomized patients to treatment on the basis of pulse index continuous cardiac output (PiCCO)-derived parameters (one of the arterial pulse pressure waveform analysis devices described in Table 2) or control, 28-day mortality did not differ between groups.
    b. A pilot study using protocol-guided assessments of fluid responsiveness after initial resuscitation in patients with septic shock requiring vasopressors found this approach feasible and safe, paving the way for larger trials using this approach.

Patient Case

Questions 2 and 3 pertain to the following case.
A 59-year-old man with a medical history of cirrhosis complicated by ascites was transferred from the ward to the medical ICU for gross hematemesis, with an Hgb decrease from 9.2 g/dL to 7.3 g/dL, blood pressure 82/36 mm Hg, and new-onset confusion. After 2 L of lactated Ringer's solution and 2 units of PRBCs, the patient's Hgb increased to 9.1 g/dL, but he remained hypotensive. The medical team placed a PAC and an arterial blood pressure catheter, which showed the following: CVP 8 mm Hg, PCWP 14 mm Hg, CO 7.4 L/minute, and MAP 58 mm Hg.

2. With which shock state are the patient's post-resuscitation hemodynamic parameters most consistent?
    A. Hypovolemic.
    B. Obstructive.
    C. Vasodilatory.
    D. Cardiogenic.

3. After further resuscitation, the patient developed hypoxemia requiring intubation and mechanical ventilation. A post-intubation radiograph revealed diffuse bilateral alveolar opacities. The patient remained hypoxemic with an F_{IO_2} of 90% and was subsequently deeply sedated and given atracurium. The patient also remained hypotensive with low urinary output. Which best predicts that the patient will respond favorably to a fluid bolus?
    A. CVP 7 mm Hg.
    B. PCWP 11 mm Hg.
    C. SVV 16%.
    D. MAP 62 mm Hg.

E. Adequate Do_2
  1. CO, $Scvo_2$, and Svo_2
    a. Historically, CO was monitored and used as a therapeutic target in most patients with a PAC.
      i. Because treatment of general ICU patients with a PAC has not been shown to improve patient outcomes, routine use of a PAC has decreased substantially.
      ii. Use of venous oximetry ($Scvo_2$ and Svo_2) and echocardiographic findings has largely replaced use of a PAC.
    b. $Scvo_2$ may be used as a component of an early resuscitation strategy (though it is not a mandatory component).
      i. A decreased $Scvo_2$ or Svo_2 is a sign that tissue oxygen demands are not completely met by Do_2.
      ii. Strategies to increase Do_2 (and subsequently increase $Scvo_2$ or Svo_2) include fluids to optimize preload, red blood cell transfusion to increase Cao_2, and inotropes to increase CO. Because Pao_2 does not contribute significantly to Cao_2, it should not be used as a therapeutic target.
    c. If $Scvo_2$ or Svo_2 is used as a resuscitation goal, it may be more important to use predefined targets as well as trends in the early resuscitation period (first 6 hours after presentation) than in the later resuscitation periods.
    d. Caution must be used with using $Scvo_2$ or Svo_2 in isolation as a resuscitation goal for the following reasons:
      i. The assumption that decreased $Scvo_2$ or Svo_2 is synonymous with Do_2 and oxygen demand mismatch is not true because, by definition, tissue oxygen demand exceeds Vo_2 in shock.
      ii. During resuscitation, Vo_2 depends on Do_2, and increasing Do_2 will increase the Vo_2 without substantially changing $Scvo_2$ or Svo_2 until the critical Do_2 threshold is reached.
      iii. Svo_2 and CO are not directly proportional and are better described by a hyperbolic relationship. As such, in hyperdynamic states when the CO is already high, the Svo_2 will not increase substantially with increases in CO.
      iv. Venous hyperoxia may indicate mitochondrial dysfunction and impaired tissue oxygen use or shunting of blood from peripheral circulation; therefore, achieving a high $Scvo_2$ or Svo_2 is not always best.
    e. CO, $Scvo_2$, and Svo_2 are likely best interpreted as either adequate or inadequate (not high or low).
      i. Adequacy is best determined by assessing end-organ perfusion and lactate concentrations.
      ii. If CO, $Scvo_2$, or Svo_2 is inadequate, Do_2 should be raised.
    f. A strategy of systematically increasing CO to predefined "supranormal" values was not associated with a mortality benefit; hence, it is not recommended. The decision to augment CO must be individualized on the basis of organ perfusion.
  2. Lactate clearance and normalization
    a. Lactate clearance (a decrease in lactate concentration from the initial value) suggests improvement in global tissue perfusion and is associated with a decreased mortality rate.
    b. Significant discordance between lactate clearance and $Scvo_2$ may occur. In one study, 79% of patients with a lactate clearance of less than 10% had a concomitant $Scvo_2$ of 70% or greater.
    c. A protocol-based approach to resuscitating patients with sepsis or septic shock targeting a lactate clearance of at least 10% was noninferior to an approach targeting an $Scvo_2$ above 70%.
    d. Lactate normalization (to a concentration below 2 mmol/L) is a strong independent predictor of survival and may be an even better predictor of outcomes than lactate clearance.
    e. Targeting lactate clearance or normalization is an attractive end point because it does not require invasive hemodynamic monitoring.
    f. Use of lactate clearance together with $Scvo_2$ as a resuscitation goal may be best because this improves outcomes compared with use of $Scvo_2$ alone.
    g. Further discussion of lactate clearance as a resuscitation target in patients with sepsis or septic shock is included later in the chapter.

V. AGENTS USED TO TREAT SHOCK – FLUIDS AND VASOACTIVE AGENTS

A. See the Fluids, Electrolytes, and Nutrition chapter for a further discussion of fluid components.

B. The below description of fluids and vasoactive agents is specific to shock states in general. Description of agents used to treat septic shock will be discussed in section VII, Sepsis.

C. Pharmacology of Vasoactive Agents

1. Vasoactive agents can be broadly differentiated to (1) vasopressors, (2) inotropes, or (3) vasodilators. Vasoactive agents may have several of these properties.
2. Vasopressor agents are indicated if hypotension is refractory to fluid administration (the patient is no longer fluid responsive) or in the setting of severe hypotension while fluids are being administered. In addition, if a patient is severely hypotensive, vasopressors may be initiated together with additional fluid administration, even if a patient is still fluid responsive, to ensure adequate end-organ perfusion. Because there are no definitive criteria for when vasopressors should be initiated in relationship to fluid administration, bedside clinicians must often make a patient-specific assessment and decision.
3. Vasopressor agents primarily exert pharmacologic benefit by augmenting SVR. Some vasopressors may also increase CO. Table 4 highlights the receptor pharmacology of the various agents.
    a. Once the decision to start a vasoactive agent is made, a vasoactive agent or inotrope is largely selected on the basis of the agent that best achieves the desired pharmacodynamic effect(s) (e.g., increase in SVR or increase in CO). In most shock syndromes, limited literature exists to guide optimal vasoactive agent selection.
    b. Catecholamine vasopressors primarily increase blood pressure by increasing SVR through their actions on α1-receptors. Differing α_1, β_1, and β_2 activity leads to differing pharmacodynamic effects between agents, as outlined in Table 4.
    c. Vasopressin increases SVR through V_1R activity in smooth muscles resulting in vasoconstriction. Activity at V_2R receptors lead to antidiuretic hormone effects in the kidney. Selective sparing of V_1R in some vascular beds or V_2R-mediated vasodilation leads to decreased vasoconstrictive effects of vasopressin in the coronary, cerebral, and pulmonary circulation.
    d. Angiotensin II also primarily increases SVR by activating AT-R1 receptors, resulting in vascular smooth muscle contraction. Activation of AT-R1 receptors also stimulates the release of norepinephrine, vasopressin, adrenocorticotropic hormone (ACTH), and aldosterone. Activation of AT-R2 receptors can counterbalance the vasoconstrictive effects of AT-R1 in some vascular beds.
    e. Some clinicians use an initial intravenous push/bolus of vasopressors ("push dose pressors") in patients with hypotension that is either severe or expected to be short in duration (e.g., medication-associated hypotension in the setting of endotracheal intubation). Common doses include phenylephrine 100–200 mcg and norepinephrine 1–2 mcg, each given every 2–3 minutes. The efficacy and safety is unclear because few studies have evaluated this approach.

Table 4. Vasoactive Pharmacology and Pharmacodynamic Effects[a]

	DA	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Vasopressors										
Dopamine[b] < 5 mcg/kg/min	++++	0	0	0		— or ↑	— or ↑	— or ↑	↔	↔
Dopamine[b] 5–15 mcg/kg/min	0	+	++++	+		↑	— or ↑	↑	— or ↑	— or ↑
Dopamine[b] > 15 mcg/kg/min	0	++++	++	++		— or ↑	— or ↑	↑	↑	↑
Epinephrine[c] < 5–10 mcg/min	0	++	++++	+++		↑	— or ↑	↑	↑	↑
Epinephrine[c] > 5–10 mcg/min	0	++++	+++	+		↑	— or ↑	↑	↑	↑
Norepinephrine	0	++++	+++	+		↓ or — or ↑	— or ↑	— or ↑	↑	↑
Phenylephrine	0	+++	0	0		— or ↓	— or ↑	— or ↓	↑	↑
Vasopressin	N/A				V_1R and V_2R agonism	— or ↓	— or ↑	↔	↑	— or ↓
Angiotensin II	N/A				AT-R1 and AT-R2 agonism	↑	— or ↑	↔	↑	?
Inotropes										
Dobutamine	0	+	++++	++		↑	— or ↓	↑	— or ↓	— or ↓
Isoproterenol	0	0	++++	++++		↑	— or ↓	↑	— or ↓	— or ↓
Levosimendan	N/A				$Ca2^+$ sensitization and KATP activation	↔	— or ↓	↑	↓	↓
Milrinone[d]	N/A				PDE3 inhibition	— or ↑	— or ↓	↑	↓	↓

[a] Receptor activity ranges from no activity (0) to maximal (++++) activity.

[b] Dopamine has dose-dependent effects. At lower doses (< 5 mcg/kg/min), activity at dopamine receptors predominates. At moderate doses (5–15 mcg/kg/min), β_1 effects predominate, and at doses > 15 mcg/kg/min, α_1 effects predominate. However, there is overlap in these effects, and these dose ranges are not exact.

[c] Epinephrine has dose-dependent effects. At lower doses (< 5–10 mcg/min), activity at β receptors predominates. At higher doses (typically > 10 mcg/min), α1 receptor activity becomes more prominent. However, there is overlap in these effects, and these dose ranges are not exact.

[d] Normal half-life is 2.5 hr, but milrinone is eliminated renally. Loading dose rarely used in routine management.

AT-R1 = angiotensin receptor type 1; AT-R2 = angiotensin receptor type 2; DA = dopaminergic; KATP = adenosine triphosphate-sensitive potassium channels; N/A = not applicable; PDE3 = phosphodiesterase type 3; V_1R = vasopressin receptor type 1; V_2R = vasopressin receptor type 2; ? = unclear.

Information from: Bangash MN, Kong ML, Pearse RM. Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol 2012;165:2015-33; Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med 2011;183:847-55; Antonucci E, Gleeson PJ, Annoni F, et al. Angiotensin II in refractory septic shock. Shock 2017;47:560-6; Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care 2014;18:534; and Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;377:419-30; Jentzer JC, Coons JC, Link CB, et al. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015;20:249-60.

4. Inotropes exert a pharmacodynamic effect that increases CO after adequate fluid administration.
   a. Dobutamine is a β-agonist that improves cardiac function by improving SV and CO. Because of its β_1 activity, dobutamine may induce tachyarrhythmias and, given its β_2 activity, hypotension.
   b. Isoproterenol is also a β-agonist, but because it has stronger β_2 activity than dobutamine, it causes more hypotension. For this reason, isoproterenol is not commonly used in the ICU as an inotrope.
   c. Milrinone is a phosphodiesterase type 3 (PDE3) inhibitor. PDE3 inhibition potentiates cyclic adenosine monophosphate, leading to increased ventricular contractility and vasodilation.
      i. Milrinone may be desirable for patients receiving β-antagonists before critical illness or for patients having tachyarrhythmias while receiving dobutamine.
      ii. Milrinone may also be favored in patients with pulmonary hypertension (PH) because it decreases cardiac filling pressures and pulmonary vascular resistance (PVR).
      iii. Milrinone may increase or decrease blood pressure, depending on the individual patient's SVR and CO when it is administered. In general, a decrease in blood pressure is more common with milrinone than with dobutamine.
      iv. The half-life of milrinone is significantly longer (2.3–2.4 hours) than that of dobutamine (2 minutes) and isoproterenol (2.5–5 minutes) and thus limits its utilization in emergent scenarios.
   d. Levosimendan is a calcium channel sensitizer that also activates adenosine triphosphate (ATP)-sensitive potassium channels.
      i. Levosimendan's pharmacodynamic effects are similar to those of milrinone.
      ii. Like milrinone, levosimendan may be preferred in patients receiving β-antagonists before critical illness or in those with PH.
      iii. Levosimendan is not available for use in the United States.

D. Administration of Vasoactive Agents
   1. Vasopressor agents should be administered through central venous access to minimize the risk of extravasation and tissue necrosis.
   2. If central access cannot be obtained, it may be necessary to administer vasopressors peripherally until central access is established.
   3. Clinical trials comparing central and peripheral administration of vasopressors are lacking.
   4. The Surviving Sepsis Campaign (SSC) guidelines suggest initiating vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured.
   5. There are no specific guidelines on the characteristics of the peripheral access to use for peripheral vasopressor administration, but some common best practices are to use a vein proximal to the antecubital fossa, use ultrasonography to confirm intravenous placement, and administer peripherally for a short time (48 hours).
   6. If vasopressors are administered peripherally, protocolized monitoring should be developed to ensure frequent monitoring of the infusion site and for signs of extravasation.

E. Outcomes Studies
   1. Studies of therapies in patients with sepsis and septic shock will be discussed in section VII, Sepsis.
   2. Fluid and resuscitation studies in ICU patients
      a. Resuscitation fluids are commonly given for patients in the ICU, with 25%–37% of patients receiving this therapy in a 24-hour period in cross-sectional studies.

b. Crystalloids vs. colloids
   i. The Saline versus Albumin Fluid Evaluation (SAFE) study, which enrolled almost 7000 patients with varied shock types requiring fluid resuscitation, with 90% power, found no difference in 28-day mortality between treatment with 0.9% sodium chloride and 4% albumin (20.9% vs. 21.1%, p=0.87). However, this was not a study of strictly initial fluid resuscitation because the allocated study fluid was used for all fluid resuscitation in the ICU until death, discharge, or 28 days after randomization. Because of this study, crystalloids are usually preferred to albumin for the initial resuscitation of patients with shock because of their lower cost.
   ii. A pragmatic, open-label, randomized study of crystalloids compared with colloids for resuscitation found no difference between groups in 28-day mortality (27.0% vs. 25.4%, p=0.26) but did find a difference in 90-day mortality favoring the colloid group (34.2% vs. 30.2%, p=0.03). However, because 90-day mortality was a secondary (not primary) outcome, the results must be interpreted with caution. In addition, the study's open-label nature (which may bias toward finding a difference between groups) and use of many different resuscitation fluids within each study group make this study challenging to implement into practice.

c. Balanced (chloride-poor) vs. unbalanced (chloride-rich) crystalloids
   i. Administration of chloride-rich fluids may lead to afferent renal arteriole vasoconstriction, leading to a decrease in renal perfusion and kidney injury, and may cause a metabolic acidosis by lowering the strong ion difference. As such, crystalloids that better approximate the electrolyte composition of plasma ("chloride-poor," "balanced salt," or "balanced crystalloid" solutions) have been evaluated.

Table 5. Sodium and Chloride Content of Commonly Used Resuscitation Fluids

Fluid	Sodium (mmol/L)	Chloride (mmol/L)
"Chloride-rich"[a]		
0.9% sodium chloride	154	154
5% albumin	130–160[b]	0–128[b]
Hydroxyethyl starch 6% (130/0.4)	154	154
"Chloride-poor"[a]		
25% albumin	130–160[b]	0–19[b]
Lactated Ringer's solution	130	109
Plasma-Lyte A and Plasma-Lyte 148	140	98
Normosol-R	140	98

[a] Distinction between "chloride rich" and "chloride poor" is based on chloride content > or < 120 mmol/L.

[b] Differs according to manufacturer because of differences in buffer type (e.g., sodium bicarbonate or sodium chloride) and amount used. Reported chloride content of 4% Albumex (CSL Bioplasma) is 128 mmol/L, and that of 20% Albumex (CSL Bioplasma) is 19 mmol/L (products used in Australia/New Zealand), which led to the distinction of "chloride rich" and "chloride poor" for 4%–5% albumin and 20%–25% albumin, respectively. However, neither 5% Flexbumin (Baxter, Westlake Village, CA) nor 25% Flexbumin (Baxter; products available in the United States) contains chloride.

Information from: Guidet B, Soni N, Della Roca G, et al. A balanced view of balanced solutions. Crit Care 2010;14:325; Frazee EN, Leedahl DD, Kashani KB. Key controversies in colloid and crystalloid fluid utilization. Hosp Pharm 2015;50:446-53; and Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012;308:1566-72.

   ii. An open-label sequential period study evaluated outcomes between a control period in which chloride-rich fluids were routinely administered (n=760) and an intervention period in which chloride-rich fluids were restricted to attending physician approval and chloride-poor fluids were routinely used (n=773). In the intervention period, the incidence of acute kidney injury (8.4% vs. 14%, p<0.001) and use of renal replacement therapy were significantly lower (6.3% vs. 10%, p=0.005). Because the study was not blinded or randomized, the results should be considered hypothesis generating.

iii. A large, double-blind, cluster randomized, double-crossover trial, the SPLIT trial, allocated four ICUs in New Zealand to either 0.9% sodium chloride (n=1025) or a balanced crystalloid solution (Plasma-Lyte; n=1067) for all patients requiring crystalloid fluid therapy. Two crossovers occurred with 7-week intervals such that each ICU used each fluid twice during the 28-week study. A total of 2278 patients were enrolled, with 2092 patients having data available for analysis of the primary outcome of the incidence of acute kidney injury within 90 days. The balanced crystalloid solution group had no lower risk of acute kidney injury than did the 0.9% sodium chloride group (9.6% vs. 9.2%, relative risk [RR] 1.04; 95% CI, 0.80–1.36; p=0.77). There was also no difference between groups in the use of renal replacement therapy (relative risk [RR] 0.96; 95% CI, 0.62–1.50; p=0.91) or hospital mortality (RR 0.88; 95% CI, 0.67–1.17; p=0.40). Of note, this study included all fluid use (not just resuscitation fluids) as well as a primarily surgical population with a relatively low severity of patient illness and patients who received relatively low volumes of fluid overall (2 L in each group).

iv. The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) was a large, cluster-randomized, multiple-crossover, single-center trial, in which balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A; n=7942) were compared with 0.9% sodium chloride (n=7860). The median volume of fluid received in the balanced crystalloid group was 1000 mL (interquartile range [IQR] 0–3210) and 1020 mL in the 0.9% sodium chloride group (IQR 0–3500). Patients in the balanced crystalloids group had a significantly lower incidence of a major adverse kidney event (14.3% vs. 15.4%; OR 0.90; 95% CI, 0.82–0.99; p=0.04). In-hospital mortality was not significantly different between groups (10.3% vs. 11.1%, p=0.06). Of note, in a prespecified subgroup analysis, there was a greater difference in the primary outcome favoring patients who received smaller volumes of intravenous fluids; thus, the differences between fluid types are likely magnified and more significant in patients who receive larger volumes of intravenous fluids.

v. The BaSICS study was a double-blind, randomized controlled trial that compared Plasma-Lyte 148 with 0.9% sodium chloride in ICU patients requiring fluid expansion. The intervention included all fluids over 100 mL administered for fluid challenges, maintenance fluids, and drug infusions. Over 10,000 patients were included in this study. There was no difference in the primary outcome of 90-day survival (26.4% balanced solution vs. 27.2% saline; HR 0.97; 95% CI, 0.90–1.05). Of note, this study did not evaluate fluids specifically for resuscitation; rather, it evaluated any fluid volume over 100 mL.

vi. The Plasma-Lyte 148 versus Saline (PLUS) Study randomized 2037 critically ill patients from centers cross Australia and New Zealand to receipt of either Plasma-Lyte 148 or 0.9% sodium chloride as primary fluid therapy in the ICU for 90 days. No difference was detected in the primary outcome of death from any cause within 90 days (21.8% vs. 22.0%, absolute difference −0.15; 95% CI, −3.60 to 3.30). Additionally, no difference in acute kidney development or new renal replacement therapy need was detected. Similar to the aforementioned trials, the PLUS study included all fluid use, and the intervention was not limited to resuscitation fluids.

vii. A meta-analysis of 13 randomized controlled trials (n=35,884) compared the use of balanced crystalloids with 0.9% sodium chloride and found no difference in the primary outcome of 90-day mortality (RR 0.96; 95% CI, 0.91−1.01). The Bayesian analysis determined an 89.5% probability that balanced crystalloid solutions were associated with lower mortality compared with 0.9% sodium chloride.

viii. Balanced crystalloid solutions may lead to hyponatremia (with lactated Ringer's solution) or cardiotoxicity (with acetate-containing solutions) when administered in large volumes. Caution should be used with these solutions in patients with brain injury because of the risk of cerebral edema and in those with hyperkalemia because they contain potassium (lactated Ringer solution contains 4 mmol/L of potassium, Plasma-Lyte A contains 5 mmol/L of potassium).

d. Hydroxyethyl starch solutions should not be used for fluid resuscitation in the ICU.
   i. A study of 7000 critically ill patients requiring fluid resuscitation compared a low-molecular-weight, low-molar-substitution (130/0.4) hydroxyethyl starch solution with 0.9% sodium chloride. Ninety-day mortality between the hydroxyethyl starch and 0.9% sodium chloride groups did not differ (18.0% vs. 17.0%, p=0.26), but patients allocated to hydroxyethyl starch had a greater need for renal replacement therapy (7.0% vs. 5.8%, p=0.04) and a higher incidence of adverse events (5.3% vs. 2.8%, p<0.001).
   ii. A systematic review and meta-analysis that analyzed only unbiased trials found an association between hydroxyethyl starch use and increased patient mortality (RR 1.09; 95% CI, 1.02–1.17; p=0.02) and need for renal replacement therapy (RR 1.32; 95% CI, 1.15–1.50; p<0.001).

3. Vasopressors and inotropes in shock
   a. A multicenter randomized trial, the SOAP II trial, included patients requiring vasopressors for shock of any type and excluded those requiring vasopressors for more than 4 hours before enrollment. Enrolled patients were allocated to either blinded norepinephrine or dopamine. Twenty-eight–day mortality between patients receiving dopamine and those receiving norepinephrine did not differ (52.5% vs. 48.5%, p=0.10), but patients receiving dopamine more often developed an arrhythmia (24.1% vs. 12.4%, p<0.001), required open-label norepinephrine (26% vs. 20%, p<0.001), and had fewer open-label vasopressor-free days (12.6 days vs. 14.2 days, p=0.007).
      i. A predefined subgroup analysis evaluated the influence of shock type on the outcome. Patients with cardiogenic shock allocated to dopamine had a higher mortality rate than those allocated to norepinephrine (log-rank p=0.03). However, the overall effect of treatment did not differ among the shock subgroups (interaction p=0.87), suggesting that the reported differences in mortality according to subgroup are spurious.
      ii. These data suggest that although norepinephrine does not improve mortality compared with dopamine, it is safer and more effective at increasing a patient's blood pressure. Given these data, a case could be made for norepinephrine as the first-line vasoactive medication of choice in all shock types.
   b. A multicenter randomized trial comparing norepinephrine with epinephrine for patients with undifferentiated shock found no difference between agents in the time to achieving a goal MAP (median 40 hours vs. 35.1 hours, p=0.26) or median number of vasopressor-free days at day 28 (25.4 days vs. 26.0 days, p=0.31). However, patients allocated to epinephrine had higher heart rates and lactic acid concentrations on the first study day (but not on subsequent days) and were more often withdrawn from the study by the treating clinician (12.9% vs. 2.8%, p=0.002). These data suggest that epinephrine has no efficacy benefits over norepinephrine and is associated with an increased incidence of adverse effects.
   c. In a systematic review and meta-analysis of vasopressors for patients with circulatory shock of all types, all-cause mortality did not differ in any comparison of different vasopressor agents or combinations.
      i. Single vasopressors evaluated included norepinephrine (reference group), dopamine, epinephrine, terlipressin, vasopressin, and phenylephrine. Vasopressor combinations included norepinephrine plus dobutamine and norepinephrine plus dopexamine (which were compared with epinephrine).

    ii. Participants treated had more arrhythmias with dopamine than with norepinephrine. The authors concluded that major changes to clinical practice are not needed but that selection of vasopressors could be better individualized and could be based on clinical variables reflecting hypoperfusion. This systematic review is limited by the small number of patients enrolled in randomized studies of some agents (e.g., phenylephrine) and few studies with combination therapy.

d. Angiotensin II is a novel vasopressor agent being evaluated for patients with vasodilatory shock.
    i. In a phase III study of patients with shock (the Angiotensin II for the Treatment of High-Output Shock [ATHOS-3] study) (n=321) without evidence of a low CO (about 90% with sepsis), use of angiotensin II, compared with placebo, more often led to a MAP response (MAP of 75 mm Hg or greater or MAP increase of 10 mm Hg or greater, without an increase in open-label vasopressor dose) at hour 3 (69.9% vs. 23.4%, p<0.001). Angiotensin II significantly reduced the cardiovascular Sequential Organ Failure Assessment (SOFA) subscore at hour 48, but not the total SOFA score. Patients in the angiotensin II group more often developed a thrombotic event (12.9% vs. 5.1%, p=0.02), a new infection (30.1% vs. 19.0%, p=0.029), and delirium (5.5% vs. 0.6%, p=0.036).
    ii. A post hoc analysis of patients from the ATHOS-3 study with acute kidney injury requiring renal replacement therapy found that patients treated with angiotensin II had longer survival (adjusted hazard ratio [HR] 0.44; 95% CI, 0.24–0.80) and were more likely to discontinue renal replacement therapy within 7 days (adjusted HR 2.90; 95% CI, 1.29–6.52) than those who received placebo.
    iii. One retrospective study evaluating angiotensin II use found that of the 270 included patients, 67% had a positive hemodynamic response 3 hours after its initiation. Of note, 92% of patients were also receiving vasopressin at the time of angiotensin II initiation.
    iv. These evaluations suggest that angiotensin II is an effective vasopressor for patients with vasodilatory shock, particularly in those with acute kidney injury, but outcomes-based studies are needed before this agent is implemented into routine clinical practice.
    v. Because of the increased risk of thrombosis associated with angiotensin II, concurrent venous thromboembolism prophylaxis is recommended.

e. Levosimendan
    i. In a study of patients with sepsis, adding blinded levosimendan for 24 hours compared with placebo did not lead to a significant difference in the mean SOFA score (6.68 ± 3.89 vs. 6.06 ± 3.89, respectively, p=0.053). Mortality at 28 days also did not differ between the levosimendan and placebo groups (34.5% vs. 30.9%, p=0.43). Patients in the levosimendan group more often developed a supraventricular tachyarrhythmia (3.1% vs. 0.4%, p=0.04).
    ii. A study of levosimendan compared with placebo for 48 hours in patients with circulatory shock after cardiac surgery was terminated early for futility. Thirty-day mortality did not differ between the levosimendan and placebo groups (12.9% vs. 12.8%, p=0.97), nor did the groups differ in duration of mechanical ventilation or incidence of cardiac arrhythmias.
    iii. These data suggest that levosimendan does not improve outcomes in patients with sepsis or circulatory shock after cardiac surgery and should not be used in these patients.

Patient Case

Questions 4 and 5 pertain to the following case.
J.B. is a 28-year-old man (weight 92 kg) who presented to the surgical ICU with shock after an appendectomy was complicated by appendiceal perforation. In the operating room, the patient received 2 L of lactated Ringer's solution and 500 mL of 5% albumin and was initiated on norepinephrine. The patient is still receiving norepinephrine 12 mcg/minute (0.13 mcg/kg/minute) with a lactate of 6.8 mmol/L and had a CO increase of 18% with a PLR.

4. Which would best meet J.B.'s fluid needs?
   - A. 5% albumin.
   - B. 6% hydroxyethyl starch.
   - C. 0.9% sodium chloride.
   - D. No fluids necessary.

5. After 12 hours in the surgical ICU, J.B. remains hypotensive with a lactate concentration of 5.2 mmol/L. He currently requires norepinephrine 14 mcg/minute (0.15 mcg/kg/minute); his MAP is 64 mm Hg and $Scvo_2$ is 61%. A bedside echocardiogram done by the ICU team reveals large ventricles with poor contractility. Which action is best?
   - A. Start phenylephrine.
   - B. Start vasopressin.
   - C. Increase norepinephrine.
   - D. Start epinephrine.

VI. VASODILATORY AND DISTRIBUTIVE SHOCK

A. Etiology and Epidemiology
   1. *Vasodilatory shock* broadly describes tissue hypoperfusion secondary to a decrease in SVR or hypoperfusion despite a normal or elevated CO, whereas *distributive shock* is technically a subset of vasodilatory shock that describes maldistribution of blood flow at the level of microcirculation (shunting) or at the organ level. However, this differentiation is likely trivial because distributive shock usually exists in vasodilatory shock, and the terms are often used interchangeably.
   2. Vasodilatory shock is the most common type of shock, with about 66% of the patients requiring vasoactive medications having this shock type.
   3. Septic shock is the most common cause of vasodilatory shock, but this shock type may also occur in several other conditions, including immune-mediated ("anaphylactic") and nonimmunologic ("anaphylactoid") reactions, neurogenic shock (classically secondary to spinal cord injury), intoxication, peridural or epidural infusion, adrenal insufficiency (Addisonian crisis), and thyroid insufficiency (myxedema coma) or as a component of ischemia-reperfusion injury (e.g., after cardiac arrest or cardiopulmonary bypass). Vasodilatory shock also occurs because of prolonged severe hypotension from any initial shock type (vasodilation is a final common pathway).
   4. The three most common causes of vasodilatory shock are septic shock (which will be covered in detail in section VII, Sepsis), immune-mediated (anaphylactic) shock, and neurogenic shock.

B. Pathophysiology
  1. Vasodilatory shock occurs because of a failure of the vascular smooth muscle cells to constrict, whether from a failure of vasoconstriction methods or the inappropriate activation of vasodilatory mechanisms. In most cases (except for neurogenic shock), this failure occurs despite high plasma concentrations of endogenous vasoconstrictors (e.g., norepinephrine, epinephrine, and angiotensin II).
  2. Potential mechanisms of vasodilation
    a. Activation of cellular ATP-dependent potassium channels leads to hyperpolarization of the vascular smooth muscle cell through potassium efflux, which prevents extracellular calcium influx by voltage-gated calcium channels. As a result, cellular depolarization is prevented, high cytosolic calcium concentrations needed for vasoconstriction are not achieved, and vasodilation occurs.
    b. Increased expression of inducible nitric oxide synthase leads to increased intracellular nitric oxide concentrations and resultant vasodilation by a cyclic guanosine monophosphate–mediated mechanism. Nitric oxide may also induce vasodilation by activating potassium channels in the plasma membrane, leading to cellular hyperpolarization, as described earlier.
    c. Inappropriately low plasma vasopressin concentrations despite the level of shock ("relative vasopressin deficiency") may contribute to the inability of the vascular smooth muscle cell to contract. Although initial plasma vasopressin concentrations may be high in the initial setting of shock, vasopressin concentrations may decrease to physiologic concentrations as quickly as 1 hour after the onset of hypotension.
  3. The pathogenesis of vasodilation depends on the underlying cause.
    a. Septic shock involves complex interactions between an infecting pathogen and the host inflammatory, immune, and coagulation response. The pattern-recognition (e.g., toll-like) receptors on innate immune system cells recognize specific molecules present in microorganisms and signal the release of nuclear factor B, which leads to the transcription of both proinflammatory cytokines (e.g., interleukin-1, interleukin-6, tumor necrosis factor alpha) and anti-inflammatory cytokines (i.e., interleukin-10). These proinflammatory cytokines activate neutrophils and endothelial cells, leading to an increased expression of inducible nitric oxide synthase and subsequent vasodilation.
    b. Neurogenic shock involves a decrease in sympathetic outflow from the central nervous system with unopposed parasympathetic activity. As such, vascular tone is lost, resulting in a decrease in SVR and venous pooling of blood with a subsequent decrease in preload. Concomitant bradycardia is common, and decreased CO (even after fluid administration) may occur because of the interruption of cardiac sympathetic innervation, further contributing to hypotension. This shock type classically occurs as a complication of an acute spinal cord injury at the level of the thoracic or cervical vertebra, most commonly when the injury is above the fifth cervical vertebra.
    c. Immune-mediated (anaphylactic) shock occurs because of reexposure to a sensitizing foreign pathogen that stimulates immunoglobulin E–mediated mast cell or basophil degranulation and resultant cytokine (e.g., histamine and tryptase) release. The mechanism of vasodilation is complex and multifaceted; however, for example, the binding of histamine to the histamine-1 receptor can activate nitric oxide synthase with resultant increases in nitric oxide and vasodilation.
  4. Profound vasodilation leads to ineffective circulating plasma volume (either from venodilation ["venous pooling"] or from fluid shifts because of increased vascular permeability) and resultant decreases in cardiac preload and CO.

C. Resuscitation and Treatment
  1. Resuscitation and treatment of patients specifically with sepsis and septic shock is covered later in the chapter.
  2. The underlying cause of the shock state must quickly be addressed when resuscitation is initiated.
    a. Septic shock requires rapid (within 1 hour of disease recognition) administration of antimicrobials with activity against all likely pathogens.

    b. The potential offending agent should be discontinued (for medication-related reactions) and potentially removed (in the setting of envenomation) for patients with immune-mediated (anaphylactic) shock.

3. Treatment goals and end points of resuscitation are usually similar to those listed in section IV, Resuscitation Parameters and End Points. In the setting of acute spinal cord injury, a MAP goal of at least 85 mm Hg has been associated with improved outcomes in uncontrolled studies. As such, the guidelines recommend an initial MAP goal of 85–90 mm Hg in patients with acute spinal cord injury for 1 week after injury (level III recommendation).
4. Initial resuscitation
    a. The treatment of choice is intravenous fluids, which restore effective circulating volume.
        i. Crystalloids (e.g., lactated Ringer solution or normal saline) are typically the initial fluid of choice compared with colloids (e.g., albumin or other blood products).
        ii. Fluid should be administered until the patient is no longer fluid responsive.
    b. Vasopressors should be initiated for hypotension unresponsive to fluid administration.
        i. Norepinephrine is usually considered the first-line vasopressor because of its ability to increase SVR without decreasing CO.
        ii. Epinephrine is typically used for patients with immune-mediated (anaphylactic) shock to provide mast cell stabilization, histamine suppression, bronchodilation, and vasoconstriction. During initial treatment, intramuscular epinephrine (0.01 mg/kg; maximum 0.5 mg) into the anterolateral thigh is preferred for speed and fewer adverse events, including overdoses, compared with intravenous epinephrine. Intramuscular epinephrine may be repeated at 5- to 15-minute intervals if the response is inadequate. Beyond initial management, in patients who continue to be hypotensive despite intramuscular epinephrine, epinephrine infusions (1–10 mcg/minute) are often used for ongoing shock, largely because of convention rather than evidence. In patients with actual or impending cardiac arrest, slow, intravenous administration of epinephrine 50 mcg may be necessary. Norepinephrine, vasopressin, and other vasopressor agents have been used with refractory hypotension associated with anaphylaxis, though it is unclear whether this strategy is superior to epinephrine alone. Dosing and route of administration of epinephrine for anaphalaxis should be monitored closely and verified; accidental overdoses involving decimal errors or confusing “mcg” with “mg” have led to adverse events such as cardiac arrest.
        iii. In neurogenic shock, agents with combined vasoconstrictive and inotropic properties (e.g., norepinephrine, dopamine, epinephrine) are preferred. Phenylephrine may also be used, but a concomitant inotropic agent (e.g., dobutamine) is often administered.
            (a) Atropine may also be given for symptomatic bradycardia.
            (b) Adjunctive oral pseudoephedrine or midodrine may also be used to maintain a MAP greater than 85 mm Hg for 1 week.
5. Additional therapies
    a. Immune-mediated (anaphylactic) shock is also conventionally treated with concomitant histamine-1 and histamine-2 receptor antagonists and corticosteroids, though no strong data support the use of these agents. Corticosteroids have a slow onset of action (4–6 hours) and are therefore ineffective for acute management; however, they may decrease the risk of late symptoms. If used, methylprednisolone 1–2 mg/kg or the equivalent is recommended.
    b. The most recent guidelines regarding the treatment of patients with acute cervical spine and spinal cord injuries recommend against administering methylprednisolone (level I recommendation).
    c. Patients with vasodilatory shock secondary to adrenal insufficiency (Addisonian crisis) should receive intravenous corticosteroids (typically hydrocortisone 50 mg every 6 hours).
    d. Management of vasodilatory shock secondary to thyroid insufficiency (myxedema coma) is outlined in the Hepatic Failure/GI/Endocrine Emergencies chapter.

VII. SEPSIS

A. Introduction
  1. Sepsis is caused by a dysregulated host response to infection.
  2. While continuing to evolve, the diagnosis of sepsis traditionally has required a known or suspected source of infection with two or more criteria of the systemic inflammatory response syndrome. Sepsis was further classified as sepsis, severe sepsis (sepsis with organ dysfunction), or septic shock (sepsis with arterial hypotension unresponsive to fluid administration).

B. Definitions
  1. The SSC, a joint collaboration between the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, has published five iterations of international guidelines for the treatment of patients with sepsis and septic shock. The 2021 SSC guidelines were sponsored or endorsed by 24 international organizations and inform many of the recommendations in this section.
  2. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
  3. Organ dysfunction can be identified as an acute change in the total SOFA score of 2 points or higher consequent to the infection.
  4. A prompt identification tool ("qSOFA") for bedside use outside the ICU was also proposed in 2016, which includes altered mental status, SBP of 100 mm Hg or less, and respiratory rate of 22 breaths/minute or greater. Fulfillment of two of these three criteria had predictive validity for mortality similar to the full SOFA score outside the ICU (technically, a Glasgow Coma Scale score of 13 or less was used in the regression model but was simplified to any alteration in mental status for the qSOFA).
     a. Of importance, qSOFA does not define sepsis, but two or more qSOFA criteria are a predictor of both increased mortality and ICU stays of more than 3 days in non-ICU patients. These criteria should also be used to investigate further for infection.
     b. The full SOFA score is superior to the qSOFA for predicting mortality in patients in the ICU.
     c. Emerging data analyses suggest that in patients outside the ICU, the qSOFA score has a lower discriminant ability for predicting ICU admission or death than other early warning scores (NEWS or MEWS) and should be further investigated before implementation as a risk-stratification tool for patients with suspected infection.
     d. Because data are lacking to support its use as a screening tool, the 2021 SSC guidelines recommend against using qSOFA as a single screening tool for sepsis or septic shock.
  5. Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are sufficient to increase mortality substantially.
  6. Patients with septic shock can be identified as those with sepsis with persistent hypotension requiring vasopressors to maintain a MAP of 65 mm Hg and greater and having a serum lactate concentration greater than 2 mmol/L despite adequate fluid resuscitation.
  7. With this new definition, the systemic inflammatory response syndrome criteria are no longer used, and severe sepsis no longer exists as a clinical entity.
  8. The new sepsis definition better identifies patients at risk of in-hospital mortality secondary to sepsis (about 10% mortality) than the previous definition.
  9. These definitions will likely shift patient identification and terminology in clinical practice, particularly for patient inclusion in studies.
  10. The SSC bundles are no longer included in the SSC guidelines, but they are published on the SSC website (www.survivingsepsis.org). This website also contains the most up-to-date recommendations, tools for implementation, and official statements from the campaign regarding ongoing events (e.g., the new sepsis definitions).

C. Epidemiology and Social Determinants of Health
   1. Sepsis is common, with an annual incidence in the United States above 890,000, rising by about 13% per year, and an associated cost exceeding $24 billion.
   2. In a European epidemiologic study, 37% of all ICU patients had sepsis.
   3. Septic shock is the most common shock type, accounting for 62% of all cases of shock syndromes requiring vasopressors.
   4. In-hospital mortality associated with severe sepsis and septic shock (using previous definitions) is around 18%–25%, whereas mortality at 2 years is around 45%.
   5. In-hospital mortality of patients with septic shock defined according to the new definition was 35%–54% in large retrospective data sets.
   6. Many disparities exist with sepsis incidence, complications, and mortality in at-risk, minority, and underserved communities and populations.
      a. American Indians and Alaskan Natives are 1.6 times more likely to die from sepsis than all other races in the United States.
      b. Asian and Pacific Islander patients are 16% more likely to die from sepsis than White patients.
      c. Black patients are 1.7 times more likely to develop severe sepsis than White patients.
      d. Hispanic patients are 10% more likely to develop severe sepsis than White patients.

D. Pathophysiology
   1. Sepsis and septic shock involve complex interactions between an infecting pathogen and the host inflammatory, immune, and coagulation response.
   2. Hypotension develops through the inappropriate activation of vasodilatory mechanisms (increased nitric oxide synthesis) and the failure of vasoconstrictive pathways (activation of ATP-dependent potassium channels in vascular smooth muscle cells and vasopressin deficiency), resulting in a vasodilatory shock. In addition, blood flow is inappropriately dispersed at the organ level or in the microcirculation (shunting), leading to distributive shock.
   3. Vascular endothelial cell injury leads to capillary fluid leak and a resultant decrease in preload. Venous dilation further exacerbates the decrease in cardiac preload.
   4. Tissue DO_2 may further be impaired by a decrease in CO, inadequate CaO_2 (low hemoglobin concentration or saturation), or impaired oxygen unloading from hemoglobin. These multifactorial hemodynamic abnormalities lead to decreased effective tissue perfusion, in which VO_2 exceeds DO_2 and cellular injury results. This further compounds the proinflammatory and procoagulant state, precipitating multiple organ dysfunction and possibly death.

E. Diagnosis
   1. There is no specific diagnostic test for sepsis or septic shock, and the diagnosis is typically based on the definitions noted earlier.
   2. Recognizing that pneumonia is the most common site of infection (in about 45% of cases), followed by intra-abdominal infection (about 30%) and urinary tract infection (about 11%), microbial cultures should be sent from all suspected infectious sites as soon as possible.
   3. All microbial cultures are negative in more than 25% of cases, and only 30% of patients have positive blood cultures. The most commonly isolated pathogens in ICU patients are gram-negative bacteria (62%), gram-positive bacteria (47%), and fungi (19%).
   4. Cultures should be obtained before antimicrobial therapy is initiated unless doing so would significantly delay (greater than 45 minutes) therapy.

F. Treatment of Sepsis and Septic Shock
   1. The pharmacologic-related 2021 SSC recommendations can be found in Box 1

Box 1. Pharmacologic-Related Surviving Sepsis Campaign Recommendations for Patients with Sepsis and Septic Shock[a]

Initial Resuscitation

1. Sepsis and septic shock are medical emergencies, and treatment and resuscitation are recommended to begin immediately (BPS)
2. For patients with sepsis-induced hypoperfusion or septic shock, at least 30 mL/kg of IV crystalloid fluid is suggested to be given within the first 3 hr of resuscitation (weak recommendation, low quality of evidence)
3. Dynamic measures to guide fluid resuscitation are suggested over physical examination or static parameters alone (weak recommendation, very low quality of evidence)
4. Guiding resuscitation to decrease serum lactate in patients with elevated lactate level is suggested (weak recommendation, low quality of evidence)
5. Capillary refill time to guide resuscitation as an adjunct to other measures of perfusion is suggested (weak recommendation, low quality of evidence)
6. An initial target MAP of 65 mm Hg is recommended in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence)

Antimicrobial Therapy

1. In patients with possible septic shock or a high likelihood of sepsis, administering antimicrobials immediately, ideally within 1 hr of recognition, is recommended (strong recommendation, low quality of evidence for septic shock; very low quality of evidence for sepsis without shock)
2. In patients with possible sepsis without shock, rapid assessment of the likelihood of infectious vs. noninfectious causes of acute illness is recommended (BPS)
3. A time-limited course of rapid investigation and, if concern for infection persists, the administration of antimicrobials within 3 hr from the time when sepsis was first recognized is suggested for patients with possible sepsis without shock (weak recommendation, very low quality of evidence)
4. In patients with a low likelihood of infection and without shock, deferring antimicrobials while continuing to closely monitor the patient is suggested (weak recommendation, very low quality of evidence)
5. Optimizing dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties is recommended (BPS)
6. Empiric antimicrobials with MRSA coverage are recommended in patients with sepsis or septic shock at high risk of MRSA (BPS)
7. Two antimicrobials with gram-negative coverage are suggested for empiric treatment in patients with sepsis or septic shock and at high risk for MDR organisms (weak recommendation, very low quality of evidence)
8. Double gram-negative coverage is not suggested once the causative pathogen and susceptibilities are known (weak recommendation, very low quality of evidence)
9. Empiric antifungal therapy is suggested in patients with sepsis or septic shock at high risk of fungal infection (weak recommendation, low quality of evidence)
10. Daily assessment for de-escalation of antimicrobials is suggested over using fixed durations of therapy (weak recommendation, very low quality of evidence)
11. In patients with an initial diagnosis of sepsis or septic shock and adequate source control, shorter over longer durations of antimicrobial therapy are suggested (weak recommendation, very low quality of evidence)
12. Procalcitonin in combination with clinical evaluation is suggested to decide when to discontinue antimicrobials in patients with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear (weak recommendation, low quality of evidence)

Box 1. Pharmacologic-Related Surviving Sepsis Campaign Recommendations for Patients with Sepsis and Septic Shock[a] *(continued)*

Fluid Therapy

1. Crystalloids are recommended as first-line fluid for resuscitation (strong recommendation, moderate quality of evidence)
2. Balanced crystalloids instead of normal saline for resuscitation are suggested (weak recommendation, low quality of evidence)
3. Albumin is suggested in patients who received large volumes of crystalloids (weak recommendation, moderate quality of evidence)
4. Starches are not recommended for resuscitation (strong recommendation, high quality of evidence)
5. Gelatin is not suggested for resuscitation (weak recommendation, moderate quality of evidence)

Vasoactive Medications

1. Norepinephrine is recommended as the first-line vasopressor (strong recommendation, high quality of evidence over dopamine, moderate quality of evidence over vasopressin, low quality of evidence over epinephrine)
2. Vasopressin is suggested in patients with septic shock on norepinephrine with inadequate MAP levels, instead of escalating the dose of norepinephrine (weak recommendation, moderate quality of evidence)
3. Epinephrine is suggested in patients with septic shock and inadequate MAP levels despite norepinephrine and vasopressin (weak recommendation, low quality of evidence)
4. For patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, either adding dobutamine to norepinephrine or using epinephrine alone is suggested (weak recommendation, low quality of evidence)
5. Adding dobutamine to norepinephrine or using epinephrine alone is suggested in patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure (weak recommendation, low quality of evidence)
6. Starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured is suggested (weak recommendation, very low quality of evidence)

Corticosteroids

1. Corticosteroids are suggested for patients with septic shock and an ongoing requirement for vasopressor therapy (weak recommendation, moderate quality of evidence)

[a] Strength and evidence level of recommendations listed in parentheses are according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The system classifies strength of recommendations as strong or weak and quality of evidence as high, moderate, low, or very low. BPSs represent ungraded strong recommendations developed using strict criteria.

BPS = best practice statement; IV = intravenous(ly); MAP = mean arterial pressure; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*.

Information from: Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med 2021;49:e1063-e1143.

2. Early recognition and treatment of patients with sepsis, particularly those with sepsis-induced end-organ hypoperfusion, is of utmost importance.
3. Initial resuscitation
   a. Initial goals of therapy are to restore effective tissue perfusion (by administering intravenous fluids and vasoactive medications) while treating the underlying cause of the syndrome (through antimicrobial administration and infectious source control, as applicable).
   b. Patients should first be administered a fluid challenge of 30 mL/kg of crystalloid solution as quickly as possible.
   c. Over the years, quantitative resuscitation has been evaluated in several clinical studies and is no longer recommended for routine use in patients with sepsis or septic shock.
      i. This strategy includes intensive monitoring (e.g., placement of a central venous [superior vena cava] catheter or echocardiography), setting goals for hemodynamic support, and using therapies to achieve those goals (e.g., use and optimization of fluids, vasopressors, and Do_2 methods).
      ii. Instead, further resuscitation should be guided by reassessment of hemodynamic parameters.
      iii. Quantitative resuscitation strategies have been evaluated in several large studies.
         (a) "Early goal-directed therapy"
            (1) The landmark study of early goal-directed therapy evaluated 263 patients with sepsis and septic shock treated in the ED for the first 6 hours after presentation.
            (2) Treatment of patients in the standard therapy group was at the clinician's discretion, whereas treatment of those in the intervention arm uniformly incorporated a protocol to achieve the previously mentioned goals and incorporated Scvo2 as a treatment goal (70% or greater).
            (3) Early, aggressive, goal-directed resuscitation was associated with a 16% absolute risk reduction in hospital mortality compared with standard therapy (30.5% vs. 46.5%, p<0.009).
            (4) Critiques of this study include a higher-than-expected mortality rate in the standard therapy arm, the incorporation of CVP as a resuscitation goal, and the study's single-centered nature.
            (5) Many centers faced logistical and financial barriers to implementing the early goal-directed therapy protocol. As such, alternative approaches to quantitative resuscitation were developed and studied.
         (b) Protocolized Care for Early Septic Shock (ProCESS) study
            (1) Randomized 1341 ED patients with septic shock in U.S. academic medical centers to three treatment arms:
               - Early goal-directed therapy (with the same protocol as noted previously)
               - Protocol-based standard care that did not require use of a central venous catheter but that used clinician judgment for fluid administration and hypoperfusion, together with a shock index (heart rate/SBP) of less than 0.8 and an SBP greater than 100 mm Hg as resuscitation targets
               - Usual care (treatment according to the bedside physician)
            (2) 60-day mortality did not differ between the treatment arms (early goal-directed therapy 21.0% vs. protocol-based standard care 18.2% vs. usual care 18.9%, p=0.55, for the three-group comparison).
            (3) Patients in the early goal-directed therapy arm were more often admitted to the ICU (91.3% vs. protocol-based standard care 85.4% vs. usual care 86.2%, p=0.01).
            (4) This study has several critiques, primarily a likely shift of usual care toward therapy that resembles quantitative resuscitation (both of which may have contributed to a type II error).

(c) Australasian Resuscitation in Sepsis Evaluation (ARISE) study
  (1) Randomized ED patients in both academic and nonacademic centers mainly in Australia and New Zealand to either early goal-directed therapy (with the same protocol noted previously) or usual care (treatment according to the bedside physician)
  (2) 90-day mortality did not differ between the treatment arms (early goal-directed therapy 18.6% vs. usual care 18.8%, p=0.90).
  (3) Because the enrolled patients had lower severity-of-illness scores and lower mortality at 90 days, they may have been less acutely ill than the patients enrolled in the ProCESS trial. However, about 70% of the patients in the ARISE study had septic shock at randomization (only 54% of the patients in the ProCESS trial met this criterion), suggesting the patients in ARISE were critically ill and the intended population was studied.

(d) Protocolised Management in Sepsis (ProMISe) study
  (1) Randomized 1260 ED patients in both academic and nonacademic centers in England to either early goal-directed therapy or usual care (identical to the ARISE study in design)
  (2) 90-day mortality did not differ between those treated with early goal-directed therapy and those treated with usual care (29.5% vs. 29.2%, p=0.90).
  (3) Patients in the early goal-directed therapy arm had higher SOFA scores at 6 hours (mean 6.4 ± 3.8 vs. 5.6 ± 3.8, p<0.001), more often received advanced cardiovascular support (37.0% vs. 30.9%, p=0.026), and had a longer ICU length of stay (median [IQR] 2.6 [1.0–5.8] days vs. 2.2 [0.0–5.3] days, p=0.005).

(e) Discussion of ProCESS, ARISE, and ProMISe studies
  (1) In a systematic review and meta-analysis that included the ProCESS, ARISE, and ProMISe studies, early goal-directed therapy was not associated with a difference in mortality compared with control (OR 1.01; 95% CI, 0.88–1.16; p=0.9), but it was associated with increased vasopressor use (OR 1.25; 95% CI, 1.10–1.41; p<0.001) and more frequent ICU admission (OR 2.19; 95% CI, 1.82–2.65; p<0.001).
  (2) Patients in these studies received about 30 mL/kg of crystalloid solution before study enrollment. This is significantly different from the patients in the landmark early goal-directed therapy study, in which patients were enrolled before resuscitation.
  (3) The ARISE and ProMISe studies required antimicrobial administration before enrollment. In ProCESS, 76% of patients had antimicrobials administered before enrollment and 97% within 6 hours of enrollment. In the landmark early goal-directed therapy study, only 86% of patients had antimicrobials administered within 6 hours of enrollment.
  (4) These studies highlight the benefits of timely administration of antibiotics and intravenous fluids, which should be a focus of the early care of patients with sepsis and septic shock.
  (5) 51%–62% of patients in the usual care arms of these studies had a central venous catheter inserted, even though it was not required in the study protocol.
  (6) The consistent findings of lower mortality rates in the contemporary studies suggest that care of patients with septic shock has evolved since the landmark early goal-directed therapy study.
  (7) In centers with ubiquitous early recognition and aggressive resuscitation strategies, protocolized care may no longer be mandatory.
  (8) Restrictive fluid approach

- Recent studies have evaluated approaches of restricting early fluid resuscitation in patients with septic shock.
- The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial compared clinical outcomes associated with a restrictive fluid strategy with early vasopressors to a liberal fluid strategy (consisting of 2 L crystalloid followed by additional boluses triggered by clinical markers). There was no detected difference in death before discharge home by 90 days between therapeutic strategies (absolute difference –0.9 [95% CI –4.4 to 2.6]) or other clinical outcomes.
- The 2022 CLASSIC trial randomized 1554 patients with septic shock who had received at least 1 L of intravenous fluids to either a restrictive-fluid group or a standard-fluid group in which fluid administration was protocolized and restricted to 250−500 mL of crystalloids. No difference in death by 90 days was seen between intervention arms (42.3% vs 42.1%; RR 1.00; 95% CI, 0.89−1.13) or serious adverse events (29.4% vs. 30.8%; RR 0.95; 95% CI, 0.77–1.15).

d. Lactate clearance
   i. In one study of patients with sepsis and septic shock, failure to achieve a lactate clearance of at least 10% was associated with a higher mortality rate than was failure to achieve an Scvo2 greater than 70%.
   ii. A large, multicenter, noninferiority study randomized patients to a quantitative resuscitation protocol that incorporated $Scvo_2$ as a treatment goal or to a quantitative resuscitation protocol that incorporated a lactate clearance of 10% or greater as a treatment goal.
      (a) The study aimed to address whether using Scvo2 as a treatment goal was necessary in a quantitative resuscitation protocol.
      (b) The lactate clearance strategy was noninferior to the Scvo2 strategy (in-hospital mortality 17% vs. 23%, respectively; 95% CI for mortality difference -3% to 15% [above the -10% predefined noninferiority threshold]).
      (c) Only 10% of the patients in each arm received a therapy specifically directed to improve either lactate clearance or Scvo2, which biased the study toward finding no difference between treatment arms (and incorrect rejection of a true null hypothesis of the existence of a difference between groups in this noninferiority study; a type I error).
      (d) Equally pertinent is that most patients with septic shock in this study (90%) achieved adequate Do_2 with only fluids and vasopressors.
   iii. Another multicenter, open-label study randomized ICU patients with a lactate concentration of 3 mmol/L or greater to the addition of lactate clearance of 20% or more (evaluated every 2 hours for the first 8 hours of therapy) or standard therapy (in which the treatment team was blinded for lactate concentrations).
      (a) Both treatment arms had resuscitation targets of CVP 8–12 mm Hg, MAP 60 mm Hg or greater, and urinary output above 0.5 mL/kg/hour. Scvo2 monitoring was optional in the standard therapy group but was mandated as part of the lactate clearance group. In the lactate clearance group, if the Scvo2 was 70% or greater but the lactate concentrations did not decrease by 20%, vasodilators (e.g., nitroglycerin) were initiated to improve microvascular perfusion.
      (b) Adding lactate clearance as a treatment goal was not associated with a difference in hospital mortality on bivariate analysis (33.9% vs. 43.5%, p=0.067). After adjustment for baseline differences between groups with multivariable analysis, a significant difference favored the lactate clearance group (HR 0.61; 95% CI, 0.43– 0.87; p=0.006).

        iv. Given these findings, in a low-level recommendation, the SSC suggested targeting resuscitation to decrease lactate in patients with elevated lactate concentrations as a marker of tissue hypoperfusion.
        v. A recent multicenter trial, the ANDROMEDA-SHOCK trial, randomized patients with septic shock to either peripheral perfusion-targeted resuscitation (goal capillary refill time 3 seconds) or lactate level-targeted resuscitation (goal lactate normalization or a >20% reduction in lactate every 2 hours). This study found no association between resuscitation strategy and 28 day all cause mortality (HR 0.75; 95% CI, 0.55–1.02). This trial indicates that in resource-poor settings, or when lactate cannot be readily checked, capillary refill time may be a reasonable alternative to ensure adequate perfusion in patients with septic shock.

4. Blood pressure (MAP) goal
    a. As discussed previously, MAP is the true driving pressure for peripheral blood flow and end-organ perfusion and is preferred to SBP as a therapeutic target.
    b. A multicenter, open-label study randomized patients with septic shock to resuscitation with a MAP goal of either 65–70 mm Hg (low-target group) or 80–85 mm Hg (high-target group). The higher MAP target was achieved through vasopressor administration; patients in the high-target group had a significantly higher infusion rate and duration of vasopressors than did those in the low-target group, but the groups did not differ in total volume of fluid administration. The treatment arms did not differ in 28-day mortality (34.0% in the low-target group vs. 36.6% in the high-target group, p=0.57). However, the incidence of atrial fibrillation was significantly higher in the high-target group (6.7% vs. 2.8%, p=0.02). In an a priori–defined subgroup analysis of patients with chronic hypertension (with randomization stratified according to this covariate), those randomized to the high-target group had a lower incidence of a doubling of the SCr concentration (38.9% vs. 52.0%, p=0.02, stratum interaction p=0.009) and the need for renal replacement therapy (31.7% vs. 42.2%, p=0.046, stratum interaction p=0.04).
5. Summary and recommendations for initial resuscitation
    a. After an initial fluid challenge, fluid therapy should be continued, using a fluid challenge technique, until the patient is no longer fluid responsive.
    b. Vasopressors should be applied to initially target a MAP of 65–70 mm Hg, but the MAP goal may subsequently be adjusted if adequate organ perfusion is not attained (particularly in patients with chronic hypertension).
    c. Adequate tissue Do_2 should be ensured. If a central venous catheter is not inserted, lactate clearance is a reasonable target. If a central venous catheter is inserted, a combination of markers can be used (e.g., lactate clearance and $Scvo_2$ of 70% or greater).
6. Sepsis and septic shock care bundle
    a. The SSC, in collaboration with the Institute for Healthcare Improvement, has developed a core set of process steps and treatment goals grouped into a care bundle for patients with sepsis and septic shock.
    b. The goal of the care bundle is to improve early recognition and treatment of patients with sepsis and septic shock.
    c. This SSC care bundle was updated in 2015 in response to new evidence from the three previously noted quantitative resuscitation studies (Box 2).
    d. The updated bundle acknowledges the findings of the three studies and recommends using techniques in addition to CVP and $Scvo_2$ to reassess fluid responsiveness and tissue perfusion. These techniques include either use of a repeat focused examination by a licensed practitioner to evaluate for vital signs, cardiopulmonary findings, capillary refill, pulse, and skin findings or use of at least two of the following: CVP, $Scvo_2$, bedside ultrasonography, or dynamic markers of fluid responsiveness (PLR or fluid challenge).

e. This care bundle has been adopted by the Centers for Medicare & Medicaid Services as a quality (core) measure (SEP-1).
f. The slight differences between the SSC bundle and the SEP-1 quality measure are noted in Box 2.
g. In July 2016, a letter to the editor from the SEP-1 measure stewards and a representative from the Centers for Medicare & Medicaid Services indicated that the SEP-1 measure would not be updated to correspond with the new sepsis definitions until further data are available (JAMA 2016;316:457-8).
h. Adjustment of the SSC bundle and implementation of sepsis as a quality measure have led to a shift in resuscitation approaches for many clinicians.
i. Practitioners should systematically evaluate their institutional compliance and implement broad process steps to ensure compliance with the quality measure. These steps may include, but are not limited to, patient identification by clinical decision support tools in the electronic medical record and implementation of care paths and order sets for treatment.
j. In 2018, the SSC released an update recommending that all bundle elements be completed within 1 hour to ensure that aggressive resuscitation begins immediately in patients with septic shock. At this time, this recommendation has not been adopted by the Centers for Medicare & Medicaid Services.

Box 2. Sepsis and Septic Shock Management Bundle[a]

Accomplished within 3 hr of presentation[b]

1. Measure lactate concentration
2. Obtain blood cultures before administering antibiotics
3. Administer broad-spectrum antibiotics[c]
4. Administer crystalloid 30 mL/kg for hypotension or lactate ≥ 4 mmol/L[d]

If septic shock[e] is present, additional measures to be accomplished within 6 hr of presentation[b]

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain MAP ≥ 65 mm Hg
6. If persistent arterial hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, reassess volume status and tissue perfusion, and document findings[f]
7. Re-measure lactate if the initial lactate concentration was elevated[g]

[a] Applies to all patients presenting with severe sepsis and septic shock (of note, the previous [Sepsis-2] definitions, which include the term *severe sepsis*, continue to be used for this bundle). Patients are excluded from the Centers for Medicare & Medicaid Services quality measure (SEP-1) for many reasons, including (1) they are transferred from another care facility (including an ED), (2) they have advanced directives for comfort care, (3) they have clinical conditions that preclude total measure completion (i.e., mortality within the first 6 hr of presentation), (4) they have a length of stay > 120 days, or (5) they were administered intravenous antibiotics within 24 hr of presentation. All components outlined must be fulfilled to satisfy the SEP-1 quality measure (it is an "all-or-none" measure).

[b] Time of presentation is defined as the time of triage in the ED or, if the patient is located in another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock as ascertained through chart review.

[c] Before July 1, 2021, specific antibiotics were outlined in the SEP-1 quality measure to qualify as "broad spectrum." As of July 1, 2021, any IV antibiotic satisfies the measure if given within the appropriate time.

[d] Starting January 1, 2022, the SEP-1 quality measure allows for resuscitation volumes < 30 mL/kg if appropriate documentation with rationale is recorded in the medical record as outlined in the measure documents.

[e] Septic shock defined as hypotension (to SBP < 90 mm Hg, MAP < 70 mm Hg, or SBP decrease > 40 mm Hg from known baseline) or a lactate concentration ≥ 4 mmol/L.

[f] To meet the requirements, one of the following must be documented: (1) a focused examination by a licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings; or (2) any two of the following: measure CVP, measure $Scvo_2$, bedside cardiovascular ultrasonography, or dynamic assessment of fluid responsiveness with PLR or fluid challenge.

[g] In the SEP-1 quality measure, an initial lactate concentration ≥ 2 mmol/L is considered elevated.

Information from: Surviving Sepsis Campaign (SSC). Updated Bundles in Response to New Evidence [homepage on the Internet]. Available at www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf; and The Joint Commission. Specifications Manual for National Hospital Inpatient Quality Measures. 2016. Available at https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx.

Patient Case

6. A 56-year-old woman with a medical history of hypertension presents to the ED with shortness of breath and cough productive of sputum. Her vital signs on admission are as follows: blood pressure 92/68 mm Hg, heart rate 104 beats/minute, respiratory rate 26 breaths/minute, and temperature 101.6°F (38.7°C). A chest radiograph reveals an opacity in the left lower lobe, but the radiograph is otherwise unremarkable. Her laboratory values of interest include Hgb 12.7 g/dL, WBC 16.4 × 10^3 cells/mm^3, Plt 80,000/mm^3, albumin 2.0 g/dL, lactate 3.2 mmol/L, and SCr 1.3 mg/dL. Her Glasgow Coma Scale score is 13. Which best describes the patient's condition?
   - A. Systemic inflammatory response syndrome.
   - B. Sepsis.
   - C. Severe sepsis.
   - D. Septic shock.

7. Antimicrobials
   a. Timing of initiation
      i. Adequate empiric antibiotics should be initiated within 1 hour after recognizing sepsis or septic shock.
      ii. A multicenter, retrospective study of patients with septic shock found that within the first 6 hours after the onset of hypotension, each hour of delay beyond the first hour in the administration of appropriate antibiotics was associated with a 7.6% decrease in hospital survival.
      iii. Other studies have further shown the importance of empiric antimicrobials used together with initial resuscitation, associating antimicrobial administration either before shock or within the initial hour of shock with improved survival.
   b. Initial empiric broad-spectrum therapy should include one or more drugs with activity against all likely pathogens (bacterial and/or fungal and/or viral).
      i. In an observational study of more than 5700 patients with septic shock, those who received initial appropriate antimicrobials had a significantly higher hospital survival rate than did those who received initial inappropriate antimicrobials (52.0% vs. 10.3%, $p<0.0001$).
      ii. Combination antibacterial therapy (at least two different classes of antibiotics) is indicated for patients with septic shock, but not for those with sepsis without shock.
         (a) A randomized controlled trial of patients with sepsis (termed *severe sepsis* in the study) that allocated patients to meropenem monotherapy or combination therapy with meropenem and moxifloxacin found no difference between groups in mean SOFA scores over 14 days (7.9 points vs. 8.3 points, $p=0.36$) or mortality rates at 28 or 90 days. Important caveats to this study are that the patient population studied was at a low risk of resistant pathogens (half of the patients had a community-acquired infection) and that moxifloxacin inadequately covers pathogens with a high likelihood of multidrug resistance (e.g., *Pseudomonas aeruginosa* and *Acinetobacter* spp.).
         (b) A meta-analysis that included 50 studies and more than 8500 patients with sepsis detected no overall mortality benefit of combination antibacterial therapy compared with monotherapy (pooled OR of death 0.86; 95% CI, 0.71–1.03, $p=0.09$); however, a stratified analysis showed significantly lower mortality with combination therapy in more severely ill patients (monotherapy risk of death greater than 25%, pooled OR of death with combination therapy 0.54; 95% CI, 0.45–0.66, $p<0.001$). The benefit of combination therapy was confined to patients with septic shock (with no benefit of combination therapy in patients without shock). In addition, a meta-regression analysis, which tried to elucidate

the differences in the benefit with combination therapy according to baseline mortality risk, showed a significant benefit of combination therapy in those with a mortality risk greater than 25%. These data suggest that severely ill patients benefit from combination antibacterial therapy.

iii. Combination therapy increases the likelihood that at least one drug is effective against the pathogen, particularly for known or suspected multidrug-resistant organisms such as *P. aeruginosa*.

iv. The 2021 SSC guidelines suggest combination therapy for patients at high risk of multidrug-resistant pathogens.

v. Empiric combination therapy should be de-escalated within the first few days of therapy if the patient has clinical improvement.

c. As noted in the Pharmacokinetics/Pharmacodynamics chapter, sepsis and septic shock can significantly affect the probability of attaining the antimicrobial pharmacokinetic/pharmacodynamic target. Dosing strategies for patients with sepsis should be optimized according to pharmacokinetic/pharmacodynamic principles.

i. Most notably, the volume of distribution of hydrophilic antibiotics (e.g., β-lactams, aminoglycosides, and vancomycin) will be increased. Clearance may either be increased (in the setting of augmented renal clearance) or decreased (in the presence of end-organ dysfunction).

ii. A pharmacokinetic/pharmacodynamic study of the first dose of β-lactams in patients with sepsis and septic shock suggested that the pharmacokinetic/pharmacodynamic target was attained in less than 50% of the patients given ceftazidime 2 g (28% target attainment), cefepime 2 g (16%), and piperacillin/tazobactam 4 g/0.5 g (44%). The pharmacokinetic/pharmacodynamic target was attained in 75% of patients receiving meropenem 1 g. For each antibiotic, the volume of distribution was higher and the clearance was lower than the values reported in healthy volunteers.

iii. A multicenter cross-sectional study of β-lactam concentrations in critically ill patients found that the minimum pharmacokinetic/pharmacodynamic target of at least 50% of free drug time above the minimal inhibitory concentration (MIC) (50% fT>MIC) was not achieved in 16% of patients with an infection. Of importance, achievement of 50% fT>MIC or 100% fT>MIC was independently associated with a higher likelihood of a positive outcome on multivariable analysis (OR 1.02; 95% CI, 1.01–1.04 and OR 1.56; 95% CI, 1.15–2.13, respectively).

iv. These data suggest that a loading dose approach for these antibiotics is necessary for patients with sepsis and septic shock. In addition, the impact of methods to improve the time that the free drug concentration is above the MIC should be studied further.

d. A recent retrospective analysis revealed that over 30% of patients had a delay in the second dose of antibiotics. Having a major delay in the second antibiotic dose was independently associated with increased odds of hospital mortality (OR 1.61; 95% CI, 1.01–2.57) and mechanical ventilation (OR 2.44; 95% CI, 1.24–4.69).

e. Antimicrobial therapy should be evaluated on a daily basis to determine whether opportunities for de-escalation or discontinuation exist.

i. Continued use of broad-spectrum antimicrobial therapy may cause untoward adverse effects and promote the development of resistance.

ii. De-escalation may be clear-cut in infections in which a contributive pathogen has been identified; in such cases, antimicrobial therapy should be reduced to the narrowest-spectrum agent with adequate activity. However, de-escalation may be more challenging in culture-negative sepsis.

iii. Antimicrobials are typically continued for 7–10 days, though longer courses may be indicated in patients with a poor clinical response, those with bacteremia, or those who are immunocompromised.

            iv. Procalcitonin and other biomarkers may be used to limit the duration of antimicrobial therapy and are discussed in detail in the Infectious Diseases II chapter.

8. Source control measures (e.g., drainage of an abscess, debridement of infected necrotic tissue, or removal of a potentially infected device [including intravascular access devices]), as applicable, should be done as soon as possible (within 12 hours after the diagnosis is made).
9. Fluid therapy
    a. A fluid challenge technique should be used in which fluids are administered as long as the patient has improved clinical factors (particularly end-organ perfusion).
    b. After initial resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status. Dynamic markers (instead of static markers) of fluid responsiveness should be used, when available.
    c. Crystalloids (over colloids) are the recommended initial fluid type for an initial fluid challenge and subsequent intravascular replacement in patients with septic shock.
        i. Crystalloid solutions that approximate the electrolyte composition of plasma ("balanced" solutions) are an attractive alternative to 0.9% sodium chloride, and either may be used for fluid resuscitation (see section V, Agents Used to Treat Shock, for further discussion). The 2021 SSC guidelines suggest using balanced crystalloids instead of normal saline for resuscitation in patients with sepsis and septic shock.
            (a) No prospective randomized study has directly compared 0.9% sodium chloride with balanced salt solutions for fluid resuscitation when enrollment was restricted to patients with sepsis.
            (b) A propensity-matched retrospective cohort study of medical ICU patients with sepsis found that receipt of a balanced solution compared with 0.9% sodium chloride was associated with a lower incidence of in-hospital mortality (19.6% vs. 22.8%, p=0.001). Contrary to analyses of general critical care patients, this study found no difference in the incidence of acute renal failure between groups, which leads to questions regarding the mechanism of the detected mortality difference between groups.
            (c) A systematic review and network meta-analysis of patients with sepsis suggested a lower mortality rate in patients resuscitated with balanced solutions than in patients resuscitated with 0.9% sodium chloride (OR 0.78, credibility interval 0.58–1.05; low confidence in estimate of effect), but this difference was not statistically significant.
            (d) An individual patient data meta-analysis comparing balanced crystalloids with 0.9% sodium chloride (including the aforementioned SMART study) in the patient cohort with sepsis found that mortality was not affected by fluid choice (OR, 0.94; 95% CI, 0.85-1.04). However, the probability that balanced solutions reduced the risk of new renal replacement therapy need was 97.5% in this population.
    d. Although not recommended for initial resuscitation, iso-oncotic (4%–5%) albumin may be considered in some patients.
        i. A prospectively defined subgroup analysis of the SAFE study evaluated the effect of albumin 4% compared with 0.9% sodium chloride in patients with sepsis and septic shock. The unadjusted RR of death with albumin was 0.87 (95% CI, 0.74–1.02) in patients with sepsis and 1.05 (95% CI, 0.94–1.17) in patients without sepsis (p=0.06 for heterogeneity of treatment effect by subgroup). In a multivariable analysis that accounted for baseline factors, albumin administration was associated with a lower mortality risk (OR 0.71; 95% CI, 0.52–0.97; p=0.03).

        ii. A systematic review and fixed-effect meta-analysis of albumin compared with alternative fluids for resuscitation in patients with sepsis found an association between albumin use and lower mortality (OR 0.82; 95% CI, 0.67–1.0; p=0.047). The benefit of albumin was retained when the analysis was restricted to crystalloids as the comparator (OR 0.78; 95% CI, 0.62–0.99; p=0.04). These data should be interpreted with caution, however, because many of the included studies had poor methodological quality, and when a random-effects model was used, the results for the overall analysis were not statistically significant (OR 0.84; 95% CI, 0.69–1.02, p=0.08).
        iii. These data have renewed interest in 4%–5% albumin as a resuscitation fluid for patients with sepsis and septic shock. As such, the 2021 SSC guidelines suggest albumin as a component of the fluid resuscitation regimen when patients require a substantial amount of crystalloids.
    e. Hydroxyethyl starch solutions should not be used for fluid resuscitation.
        i. Compared with patients with sepsis allocated to lactated Ringer's solution, those allocated to pentastarch (a hydroxyethyl starch formulation) had a significantly higher incidence of acute renal failure (34.9% vs. 22.8%, p=0.002) and need for renal replacement therapy (31.0% vs. 18.8%, p=0.001), with no difference in 28-day mortality (26.7% vs. 24.1%, p=0.48).
        ii. Compared with patients with sepsis randomized to receive Ringer's acetate solution, patients with sepsis randomized to receive hydroxyethyl starch had a significantly higher 90-day mortality (51% vs. 43%, p=0.03) and need for renal replacement therapy (22% vs. 16%, p=0.04).
        iii. The increased need for renal replacement therapy and lack of mortality benefit in these studies led to the strong recommendation against the use of hydroxyethyl starch for fluid resuscitation in patients with sepsis and septic shock in the 2021 SSC guidelines.
    f. Hyperoncotic (20%–25%) albumin replacement may be beneficial in patients with septic shock. An open-label study compared the replacement of albumin (with 20% albumin) to a goal serum albumin concentration of 3 g/dL plus crystalloid solution administration with the administration of crystalloid solution alone in patients with sepsis or septic shock. The albumin and crystalloid groups did not differ in the incidence of 28-day mortality (31.8% vs. 32.0%, p=0.94), but patients allocated to albumin had a shorter time to cessation of vasoactive agents (median 3 vs. 4 days, p=0.007). A post hoc subgroup analysis of patients with septic shock at enrollment showed that those randomized to albumin had a lower 90-day mortality rate (RR 0.87; 95% CI, 0.77–0.99); 90-day mortality did not differ in patients without septic shock (RR 1.13; 95% CI, 0.92–1.39; p=0.03 for heterogeneity). Of note, this post hoc subgroup analysis was performed on the secondary end point of 90-day mortality, and an analysis of the primary outcome of 28-day mortality was not reported. These data suggest that albumin replacement does not improve outcomes in patients with sepsis but that it has hemodynamic (and potentially mortality) advantages in patients with septic shock. Hence, the role of albumin replacement in patients with septic shock warrants further study.
10. Vasoactive agents and inotropes
    a. Norepinephrine is the recommended first-line vasoactive medication. A meta-analysis of randomized trials that compared norepinephrine with dopamine for the treatment of septic shock found a higher risk of short-term mortality (RR 1.12; 95% CI, 1.01–1.20; p=0.035) and arrhythmias (RR 2.34; 95% CI, 1.46–3.77; p=0.001) in patients allocated to dopamine.
    b. The optimal approach to using vasoactive agents and inotropes beyond the choice of initial vasopressor is unclear, but the choice should be based on patient-specific clinical factors.
        i. Potential interventions could include using norepinephrine monotherapy (with appropriate dose escalation) or initiating an additional therapy (i.e., a second catecholamine vasopressor, arginine vasopressin (AVP), corticosteroids, an inotrope, or a combination of these therapies).
        ii. The optimal time or norepinephrine dose at which to consider additional therapies is unknown. A dose that constitutes the failure of norepinephrine is not well defined in the literature, and the maximal doses used by clinicians (or institutions) are variable and often subjective.

c. Low-dose AVP (up to 0.03 units/minute) can be added to norepinephrine as the second-line adjunctive agent rather than escalating the dose of norepinephrine in patients not at goal MAP.
   i. In patients with septic shock, a relative vasopressin deficiency may exist, and patients may be sensitive to the vasoconstrictive effects of AVP.
   ii. Because of these effects, AVP has been used in patients with septic shock as both an endocrine replacement therapy (with a fixed-dose infusion) and a vasopressor (titrated to MAP).
   iii. The Vasopressin and Septic Shock Trial (VASST) compared the effects of adding AVP (0.01–0.03 units/minute) to norepinephrine with using norepinephrine monotherapy. Patients were initiated on the study drug an average of 12 hours after meeting the trial's inclusion criteria and when norepinephrine was at a mean dose of 20.7 mcg/minute. Overall, the study found no difference in 28-day mortality between treatment arms (35.4% vs. 39.3%, $p=0.26$), but norepinephrine requirements were significantly lower during the first 4 study days in the patients allocated to AVP ($p<0.001$). Adverse effects did not differ between groups. In an a priori–defined subgroup analysis of patients on the basis of shock severity (less severe shock defined as baseline norepinephrine dose 5–14 mcg/minute) with randomization stratified according to this covariate, 28-day mortality in the less severe shock stratum (defined as norepinephrine-equivalent doses less than 15 mcg/minute) was lower in patients randomized to AVP plus norepinephrine (26.5% vs. 35.7%, $p=0.05$), with no difference between groups in the more severe shock stratum (44.0% vs. 42.5%, $p=0.76$, stratum interaction $p=0.10$).
   iv. In the VANISH trial, which compared first-line vasopressin (up to 0.06 units/minute) with norepinephrine, there was no difference between groups in the incidence of kidney failure in survivors (absolute difference -2.3%; 95% CI, -13.0 to 8.5) or the number of kidney failure–free days in nonsurvivors (absolute difference -4 days; 95% CI, -11 to 5). Patients were initiated on the study drug within an average of 3.5 hours from shock onset and at a mean norepinephrine dose of 0.16 mcg/kg/minute. Patients were also randomized to hydrocortisone or placebo (in a 2 × 2 factorial design), but there was no significant interaction between vasopressin and hydrocortisone (interaction $p=0.98$ for 28-day mortality). Although the study intended to evaluate vasopressin as a first-line agent, 85% of patients were receiving open-label vasopressors before randomization.
   v. One consistent finding with the use of AVP in clinical trials is the reduction in norepinephrine dose requirements after its initiation, making it an attractive norepinephrine- and catecholamine-sparing agent.
   vi. Findings regarding the effects of AVP (and its analogs) on mortality have been conflicting in meta-analyses. One meta-analysis found a decreased mortality risk in patients with septic shock allocated to AVP (RR 0.87; 95% CI, 0.75–1.0; $p=0.05$), whereas another study found no significant benefit with AVP (RR 0.91; 95% CI, 0.79–1.05; $p=0.21$). Both meta-analyses found a significant benefit of AVP in decreasing norepinephrine doses. In an updated meta-analysis performed for the 2016 SSC guidelines, mortality did not differ between norepinephrine and vasopressin (RR 0.89; 95% CI, 0.79–1.00). A recent meta-analysis (which included the VANISH study) corroborated this and found no significant effect on mortality with vasopressin use (RR 0.98; 95% CI, 0.86–1.12).
   vii. The 2021 SSC guidelines note that the threshold for adding vasopressin is unclear, but it is reasonable to consider initiation when the dose of norepinephrine is 0.25–0.5 mcg/kg/minute.
   viii. High-dose vasopressin (doses above 0.03–0.04 units/minute) should be reserved for salvage therapy and, if used, should be used cautiously.

        (a) A study of patients with vasodilatory shock (about 50% with septic shock) requiring high-dose norepinephrine (greater than 0.6 mcg/kg/minute) randomized patients to AVP 0.033 units/minute versus AVP 0.067 units/minute. The study was designed to evaluate hemodynamic changes, not mortality. Patients randomized to the higher dose had a greater reduction in norepinephrine requirements than did those allocated to the lower dose ($p=0.006$). High-dose AVP did not lead to a significantly lower cardiac index than low-dose AVP (as might be expected with this pure vasoconstrictor), but this finding is difficult to interpret because most patients were receiving concomitant inotropes, and the study was likely underpowered to assess this outcome.
        (b) High-dose vasopressin is best reserved for patients with septic shock requiring high norepinephrine doses (greater than 0.6 mcg/kg/minute) with a high CO.
    ix. Despite the unclear benefits of AVP on mortality, it offers an alternative mechanism to catecholamines for vasoconstriction, and low-dose AVP is commonly used in practice (often as the second vasoactive medication).

d. The SSC guidelines suggest adding epinephrine in patients with inadequate MAP levels despite norepinephrine and vasopressin.
    i. A randomized trial of patients with septic shock compared epinephrine with norepinephrine with or without dobutamine. The groups did not differ in 28-day mortality (40% vs. 34%, $p=0.31$), but patients allocated to epinephrine had significantly higher lactate concentrations on day 1 ($p=0.003$) and lower arterial pH values on each of the first 4 study days. Caution should be used in concluding that mortality does not differ between epinephrine and norepinephrine because the study was powered to detect a 20% absolute difference in mortality rates, and a smaller difference between agents cannot be ruled out.
    ii. The benefit of adding epinephrine to norepinephrine (whether this approach has a norepinephrine-sparing effect or whether it is best used in norepinephrine failure) is unclear.
    iii. Because norepinephrine may cause tachycardia or tachyarrhythmias (often the impetus to limit doses), alternative vasopressors may be added. If catecholamine vasopressors with β_1-adrenergic properties (e.g., epinephrine) are added to augment MAP in patients receiving norepinephrine, they are unlikely to prevent tachyarrhythmias and will likely increase the risk of this adverse effect.
    iv. In addition, epinephrine may preclude the use of lactate clearance as an initial resuscitation goal because it increases lactate concentrations through increased production by aerobic glycolysis (by stimulating skeletal muscle β_2-adrenergic receptors), an effect that likely wanes with continued epinephrine administration.
    v. It seems most prudent to use epinephrine in patients receiving norepinephrine with a low MAP who require CO augmentation.

e. Phenylephrine is no longer recommended by the SSC guidelines for use in patients with septic shock because of limited clinical trial data.
    i. Because of its afterload augmentation effects without β_1-adrenergic properties, phenylephrine may theoretically decrease SV and CO. As such, it is not recommended as a first-line vasopressor in patients with septic shock who have decreased CO because of inadequate preload.
    ii. A small study ($n=32$) that randomized patients with septic shock to phenylephrine or norepinephrine as first-line therapy found no difference in hemodynamic measures (including CO) between agents in the first 12 hours of therapy. This finding is likely because of the inotropic effect of myocardial α_1-adrenergic receptor augmentation by phenylephrine. These data are in contrast to the theoretical concerns with phenylephrine and warrant further study.

    iii. During a shortage of norepinephrine in 2011, phenylephrine was used as an alternative for patients with septic shock. Compared with normal use, in-hospital mortality was higher during the norepinephrine shortage (absolute risk increase of 3.7%; 95% CI, 1.5%–6.0%; p=0.03). Because phenylephrine was the most commonly used vasoactive agent during the shortage period, phenylephrine should be used cautiously in patients with circulatory shock.
    iv. Because phenylephrine is a pure α_1-adrenergic agent, it is attractive for patients who develop a tachyarrhythmia while receiving norepinephrine. Although phenylephrine has been used in clinical practice for many years for this indication, no clinical trial data support this practice.
f. Dopamine is best used in a select patient population, including those with a low risk of tachyarrhythmias (which is difficult to predict) or those with bradycardia-induced hypotension. Low-dose ("renal dose" 2 mcg/kg/minute) dopamine should not be used to improve renal blood flow and urinary output (renal protection).
g. Preliminary data suggest that midodrine helps decrease vasopressor duration in patients in the convalescent phase of septic shock.
    i. MIDAS was a multicenter, randomized, double-blind, placebo-controlled trial of patients with hypotension admitted to an ICU requiring a single-agent vasopressor who could not be liberated from vasopressors for at least 24 hours. Patients were randomized to receive midodrine 20 mg every 8 hours or placebo. There was no difference in time to vasopressor discontinuation in the 136 included patients (23.5 hours of midodrine vs. 22.5 hours of placebo). Of note, this study was not specific for patients with septic shock.
    ii. Further, larger studies are needed before midodrine is used in routine practice.
    iii. When midodrine is used for this indication, care should be taken to ensure appropriate discontinuation after resolution of shock. Reports have noted inappropriate continuation of midodrine that may have been found in the outpatient setting.
h. Dobutamine may be indicated in patients with evidence or suggestion of myocardial dysfunction.
    i. A low CO is common in early septic shock but is often corrected with fluid resuscitation alone.
    ii. Myocardial dysfunction may persist despite fluid resuscitation, with 39% of patients having left ventricular hypokinesia on ICU admission and an additional 21% of patients developing hypokinesia 24–48 hours after ICU admission in one series.
    iii. If myocardial dysfunction leads to significantly impaired Do_2, an inotrope such as dobutamine (up to 20 mcg/kg/minute) may be indicated to improve CO.
    iv. Dobutamine should not be used to achieve a predetermined supranormal cardiac index or $Scvo_2$.
i. As noted previously, levosimendan, compared with placebo, did not lead to a significant difference in the mean SOFA score in patients with sepsis. In a meta-analysis performed by the SSC, levosimendan and dobutamine did not differ with respect to mortality (RR 0.83; 95% CI, 0.66–1.05). Given these data, dobutamine is recommended as the preferred inotrope in patients with septic shock.
j. The 2021 SSC guidelines do not recommend angiotensin II as a first-line agent because of the low quality of evidence and lack of clinical experience in sepsis; however, they note that it may play a role as an adjunctive vasopressor therapy.

Patient Case

7. A 55-year-old man presents to the medical ICU with presumed urosepsis. His medical history is significant for congestive heart failure with a baseline ejection fraction of 20%. In the medical ICU, his vital signs are as follows: blood pressure 69/45 mm Hg, heart rate 84 beats/minute, respiratory rate 32 breaths/minute, and temperature 100.6°F (38.1°C). Blood cultures are obtained, and piperacillin/tazobactam is initiated. A central venous catheter shows CVP 18 mm Hg and $Scvo_2$ 70%. Which is the most appropriate initial vasopressor for this patient?
    - A. Norepinephrine.
    - B. Vasopressin.
    - C. Dobutamine.
    - D. Epinephrine.

11. Corticosteroids should only be used in patients with septic shock who do not achieve resuscitation goals despite fluid administration and vasopressors.
    a. Corticosteroids are an attractive option for patients with septic shock because of their anti-inflammatory effects (through inhibition of nuclear factor κB) and ability to improve blood pressure response to catecholamines (through up-regulation of adrenergic receptors and potentiation of vasoconstrictor actions).
    b. Use of corticosteroids for patients with septic shock has been a source of controversy for years.
    c. In studies of short courses of high-dose corticosteroids (typically at doses of 30 mg/kg of methylprednisolone or greater) in patients with sepsis and septic shock, corticosteroids did not improve patient outcomes.
    d. Four large studies have evaluated the effect of corticosteroids in patients with septic shock, with conflicting findings on mortality.
        i. In a French trial of patients with septic shock and vasopressor-unresponsive shock (i.e., inability to increase SBP above 90 mm Hg for 1 hour despite fluids and vasopressors), patients randomized to low-dose hydrocortisone and fludrocortisone had improved survival in a time-to-event analysis (HR 0.71; 95% CI, 0.53–0.97). The mortality benefit with corticosteroids was limited to patients unable to increase their cortisol concentration by more than 9 mcg/dL in response to ACTH administration (nonresponders).
        ii. In a larger, multicenter Corticosteroid Therapy of Septic Shock (CORTICUS) study, which had less-stringent inclusion criteria than the earlier-noted French trial, hydrocortisone administration was not associated with improved survival in ACTH nonresponders (28-day mortality 39.2% vs. 36.1%, p=0.69).
        iii. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial randomized 3800 patients to hydrocortisone or placebo. 90-day mortality did not differ between the hydrocortisone or placebo groups (27.9% vs. 28.8%, OR 0.95; 95% CI, 0.82–1.10; p=0.50). However, patients randomized to hydrocortisone had quicker time to shock resolution (3 vs. 4 days; p<0.001). A subgroup analysis of patients who received hydrocortisone on the basis of time from shock onset to randomization showed improvement in death at 90 days in patients who received hydrocortisone within 6–12 hours (OR 0.71; 95% CI, 0.54–0.94).

    iv. The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial randomized 1241 patients to hydrocortisone and fludrocortisone or placebo within 24 hours of shock onset. Patients were also randomized to drotrecogin alfa (activated) in a 2 x 2 factorial design, but after the drug was withdrawn from the market, the study was continued with only the corticosteroid randomization. Patients in the hydrocortisone and fludrocortisone group had lower 90-day mortality than those receiving placebo (43.0% vs. 49.1%; RR 0.88; 95% CI, 0.78–0.99; p=0.03). In addition, patients randomized to the corticosteroid arm had increased vasopressor-free days (16 vs. 11 days; p<0.001) and organ failure–free days (14 vs. 13 days; p=0.003).
    v. These studies differed in the patient populations evaluated, with patients more severely ill demonstrating a mortality benefit from corticosteroids. When this question was specifically evaluated in the ADRENAL trial, there was no heterogeneity of effect by subgroup, suggesting severity of illness did not influence the outcome.
    vi. Other notable differences between studies that may account for the disparate results are the drug regimens used and the timing of therapy initiation.

e. Two meta-analyses that included these four studies found that corticosteroids had no mortality benefit (RR 0.96; 95% CI, 0.91–1.02 in one meta-analysis and RR 0.93; 95% CI 0.84–1.03 in another meta-analysis).

f. In meta-analyses, corticosteroid administration has consistently been associated with improvements in shock reversal and a higher incidence of adverse effects (particularly hypernatremia and hyperglycemia).

g. A recent evaluation using the Premier Healthcare Database evaluated the addition of fludrocortisone to hydrocortisone compared with hydrocortisone alone in patients with septic shock and found lower rates of the primary composite outcome of in-hospital death or discharge to hospice (47.2% vs. 50.8%; adjusted risk difference: –3.7% 95% confidence –4.2% to –3.1%) in the group of patients who received fludrocortisone. Additional data are needed to confirm the findings from this retrospective evaluation and definitively determine if the addition of fludrocortisone to the standard regimen of hydrocortisone is necessary.

h. Guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine suggest using corticosteroids in patients with septic shock. These guidelines further state that if hydrocortisone is indicated, a dose of less than 400 mg/day for 3 days or more at full dose is suggested.

i. The SSC guidelines suggest using hydrocortisone in patients with septic shock and an ongoing requirement for vasopressor therapy at a dose of 200 mg/day given as either 50 mg intravenously every 6 hours or a continuous infusion. The guidelines note the suggestion that hydrocortisone be initiated when norepinephrine or epinephrine doses exceed 0.25 mcg/kg/minute at least 4 hours after initiation.

j. Although two of the randomized controlled trials mentioned earlier used fludrocortisone, the SSC guidelines recommend hydrocortisone alone. This is likely because of the COIITSS study, a 2 x 2 factorial trial that compared hydrocortisone in combination with fludrocortisone with hydrocortisone alone. No difference in the primary outcome of in-hospital death (42.9% hydrocortisone and fludrocortisone vs. 45.8% hydrocortisone alone) or other clinical outcomes was detected between treatment arms.

k. Because of immunoassay imprecision and the inconsistent benefit of identifying patient response, the ACTH test should not be used to identify patients for corticosteroid administration.

Patient Case

8. A 62-year-old woman was admitted to the surgical ICU with presumed aspiration pneumonia. The patient has a history of insulin-dependent diabetes and hyperthyroidism. On admission, she was intubated and required aggressive resuscitation and vasopressor therapy. Currently, the patient is receiving norepinephrine 8 mcg/minute and has the following vital signs and laboratory values: blood pressure 100/60 mm Hg, heart rate 90 beats/minute, and CVP 14 mm Hg; her $Scvo_2$ is 55%. Which is best regarding the patient's steroid therapy?
   A. Administer hydrocortisone 50 mg every 6 hours.
   B. Administer hydrocortisone 8.3 mg/hour as a continuous infusion.
   C. Perform the ACTH stimulation test.
   D. No steroids are necessary right now.

12. Supportive therapies
   a. Vitamin C, hydrocortisone, and thiamine
      i. A retrospective before-after study evaluated the effect of the combination of intravenous vitamin C (1.5 g every 6 hours for 4 days or until ICU discharge), hydrocortisone (50 mg every 6 hours for 7 days or until ICU discharge, followed by a taper over 3 days), and intravenous thiamine (200 mg every 12 hours for 4 days or until ICU discharge) for patients with sepsis. Patients receiving this medication combination had a lower propensity-adjusted odds of mortality (OR 0.13; 95% CI, 0.04–0.48; p=0.002). This study is limited by the before-after design and a control group mortality rate (8.5%) lower than in contemporary sepsis studies (leading to questions about the study population).
      ii. Several subsequent randomized controlled trials have evaluated this clinical question, including the VITAMINS, VICTAS, and ACTS trials, which have all shown no benefit with the use of vitamin C, hydrocortisone, and thiamine.
      iii. Two randomized controlled trials, the CITRIS-ALI and the LOVIT trials, evaluated vitamin C without hydrocortisone or thiamine in patients with sepsis and found no clinical benefit to the use of vitamin C. In fact, the LOVIT trial found higher rates of death or persistent organ dysfunction at 28 days in the vitamin C cohort (44.5% vs. 38.5%; RR 1.21; 95% CI, 1.04–1.40).
      iv. The 2021 SSC guidelines suggest against the use of intravenous vitamin C in patients with sepsis and septic shock. They do not discuss the role of thiamine or the combination of vitamin C, hydrocortisone, and thiamine.
   b. Intravenous immunoglobulins should not be used in patients with sepsis and septic shock. In a randomized study of patients with sepsis, 28-day mortality was no different between patients allocated to intravenous immunoglobulin G and placebo (39.3% vs. 37.3%, p=0.67).
   c. A transfusion threshold of 7 g/dL or less is appropriate for patients with septic shock unless extenuating circumstances exist (i.e., myocardial ischemia, severe hypoxemia, or acute hemorrhage).
      i. A multicenter study compared two different transfusion thresholds in patients with septic shock. The study enrolled patients with septic shock and a hemoglobin concentration below 9 g/dL to receive PRBC transfusion if their hemoglobin was 7 g/dL or less (lower threshold) or 9 g/dL or less during their ICU stay.
      ii. As expected, patients allocated to the lower-threshold group less commonly received PRBC transfusion and had lower hemoglobin concentrations.
      iii. Treatment arms did not differ in 90-day mortality (43.0% in the lower threshold group vs. 36.6% in the higher-threshold group, p=0.44). Patients in the lower-threshold group had no higher incidence of ischemic events in the ICU (7.2% vs. 8.0%, p=0.64), and outcomes did not differ between groups in the subgroup of patients with chronic cardiovascular disease (RR 1.08 [95% CI, 0.75–1.40]; p=0.25 for heterogeneity of treatment effect by subgroup; only 14% of the overall population had chronic cardiovascular disease).

        iv. Although the study did not specifically evaluate the practice of transfusing blood in patients with evidence of hypoperfusion (low $Scvo_2$ or elevated lactate concentrations) associated with a low hemoglobin concentration, the median $Scvo_2$ at baseline was below 70% and lactate concentrations were above 2 mmol/L in both groups, suggesting that most patients had evidence of hypoperfusion.
        v. These data suggest that use of a hemoglobin transfusion threshold of 7 g/dL or lower is safe for most patients, including those with sepsis and septic shock.

13. Continued care of the patient with septic shock (resuscitation end points beyond first 6 hours): See section IV, Resuscitation Parameters and End Points, for an additional discussion of this topic.
    a. Uncertainty persists regarding hemodynamic targets beyond the first 6 hours of presentation.
        i. Therapy should be directed toward maintaining adequate end-organ perfusion and normalization of lactate concentrations, but the specific method(s) to achieve these goals will be patient-specific.
        ii. A strategy of systematically increasing CO to predefined “supranormal” values was not associated with a mortality benefit; hence, it is not recommended.
    b. Care should be used to avoid giving excessive fluids.
        i. In a retrospective analysis of data from a randomized controlled trial of patients with septic shock, patients in the highest quartile of fluid balance had a significantly higher mortality rate than patients in the lowest two quartiles. This association was present when fluid balance was evaluated at both 12 hours and 4 days after study enrollment. In the same analysis, a CVP greater than 12 mm Hg conferred a higher risk of mortality than a lower CVP.
        ii. A meta-analysis of 9 randomized controlled trials (n=637) that compared interventions targeted at limiting fluid administration in patients with sepsis found no difference in all-cause mortality (RR 0.87; 95% CI, 0.69−1.10) or serious adverse effects (RR 0.91; 95% CI, 0.78−1.05) with the use of lower versus higher fluid volumes.
        iii. Despite conflicting data between prospective (CLOVERS and CLASSIC) and retrospective studies, fluid administration should only be given to patients who are proven or predicted to respond to fluid. This is best accomplished using dynamic markers of fluid responsiveness.
    c. Resuscitation targeted to improving microcirculatory perfusion is a potential new therapeutic frontier.
        i. Studies have shown that the microcirculation is often altered in patients with sepsis, persistent microvascular alterations are associated with multisystem organ failure and death, alterations are more severe in non-survivors than in survivors, and improvements in microcirculatory blood flow correspond with improved patient outcomes.
        ii. Impaired microcirculatory perfusion may at least partly explain why patients have elevated lactate concentrations despite achievement of (macrovascular) hemodynamic goals.
        iii. Several strategies to improve microcirculatory perfusion have been investigated.
            (a) In a nonrandomized trial, fluid resuscitation improved microvascular perfusion in early, but not late, sepsis. Another study found that microcirculatory perfusion improved with PLR or fluid administration in patients who were fluid responsive.
            (b) Use of norepinephrine to increase the MAP above 65 mm Hg has not been associated with correction of impaired microcirculatory perfusion.
            (c) In a randomized trial of patients who underwent quantitative resuscitation, adding nitroglycerin was not associated with improved microcirculatory blood flow. In-hospital mortality was numerically higher in patients allocated to nitroglycerin than in placebo, but this difference was not statistically significant (34.3% vs. 14.2%, p=0.09).
            (d) A prospective open-label study evaluated the effects of dobutamine 5 mcg/kg/minute initiated after quantitative resuscitation (but within the first 48 hours of presentation). Dobutamine significantly improved microcirculatory perfusion compared with baseline. Of interest, the beneficial effects of dobutamine were unrelated to changes in cardiac index or blood pressure.

(e) Initiation of inhaled nitric oxide after quantitative resuscitation did not improve microcirculatory flow or lactate clearance.
(f) In summary, fluid resuscitation and dobutamine initiation appear to improve microcirculatory perfusion. It is still unknown whether using these therapies to improve microcirculatory perfusion can improve patient outcomes such as mortality.

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Agents Used to Treat Shock—Fluids and Vasoactive Agents

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: B**

The patient has hypovolemic shock caused by his upper GI hemorrhage and has symptoms of compromised end-organ perfusion (i.e., confusion). Although his history of hypertension is relevant in relation to determining a resuscitation goal, it does not acutely affect DO_2 (Answer A is incorrect). Tachycardia is a symptom in response to his hypovolemia, and, in the absence of complicating factors (e.g., atrial fibrillation or LV diastolic dysfunction), tachycardia will increase (not decrease) DO_2 (Answer C is incorrect). Leukocytosis does not impede DO_2 until it reaches an exorbitant threshold (greater than 75 L/mm^3) (Answer D is incorrect). When examining the Fick equation for DO_2, acute anemia is the determinant that is adversely affecting DO_2 (Answer B is correct).

2. **Answer: C**

The patient has evidence of vasodilatory shock post-resuscitation, with his relatively high CVP and PCWP values and high CO (Answer C is correct). This is further confirmed by a calculated SVR of 541 dynes x second x cm^{-5}. The patient could be thought to have spontaneous bacterial peritonitis in the setting of cirrhosis and ascites complicated by upper GI hemorrhage. Even though his presentation suggests hypovolemic shock (from GI hemorrhage), his MAP did not respond to fluid and blood product administration. Furthermore, he does not have low preload or low CO (Answer A is incorrect). If the patient had a low CO together with a high SVR, cardiogenic shock or obstructive shock might be possible (with one differentiation depending on CVP/right atrial pressure and PCWP), but this is untrue for the patient (Answers B and D are incorrect).

3. **Answer: C**

The patient's clinical scenario of refractory hypoxemia and hypotension with hypoperfusion suggests that an accurate prediction of fluid responsiveness is needed. Dynamic markers of fluid responsiveness (e.g., SVV) are superior to static markers of fluid responsiveness (e.g., CVP and PCWP) (Answer C is correct; Answers A and B are incorrect). A low MAP may be from either a low CO or a low SVR. Furthermore, a low preload is only one of many components that may contribute to a low CO. As such, a low MAP is not a good predictor of fluid responsiveness (Answer D is incorrect).

4. **Answer: C**

The patient has shock with hypoperfusion and a positive response to a PLR test, which suggests he is still fluid responsive (Answer D is incorrect). Data from a large randomized trial of patients with heterogeneous shock types showed no difference in efficacy and safety between albumin and 0.9% sodium chloride, but the cost of albumin is substantially higher. These data suggest that crystalloids such as 0.9% sodium chloride are preferred for fluid resuscitation in the ICU. In addition, the patient has not received a substantial volume of fluid (he has received less than 30 mL/kg; Answer C is correct; Answer A is incorrect). Hydroxyethyl starch, which has been associated with an increased need for renal replacement therapy without a mortality benefit, should be avoided for fluid resuscitation in the ICU (Answer B is incorrect).

5. **Answer: D**

The patient has evidence of ventricular dysfunction with a low $ScvO_2$ and poor ventricular contractility on echocardiogram. A vasoactive agent with strong inotropic properties is indicated. Epinephrine has strong β_1-adrenergic properties and is the best selection in this case (Answer D is correct). Both phenylephrine and vasopressin are essentially pure vasoconstrictors that do not increase CO and could theoretically decrease CO. In addition, use of phenylephrine is no longer recommended by the guidelines (Answers A and B are incorrect). Although norepinephrine has β_1-adrenergic properties, it primarily increases blood pressure through vasoconstriction secondary to its α_1-adrenergic properties, with only minimal effects on CO. Increasing norepinephrine in this case would probably not improve the patient's CO sufficiently to improve tissue perfusion (Answer C is incorrect).

6. **Answer: B**

The patient has life-threatening organ dysfunction secondary to infection. Although not all the criteria to calculate the score are available, her SOFA score is at least 4 points (2 points for Plt, 1 point for Glasgow Coma Scale score, and 1 point for SCr), indicating organ dysfunction. In addition, the patient fulfills all three qSOFA criteria (altered mental status, SBP of 100 mm Hg or less, and respiratory rate of 22 breaths/minute or greater). Therefore, she meets the criteria for sepsis, according to the new definition (Answer B is correct). Although she has an elevated lactate concentration, she does not require vasopressors to maintain a MAP above 65 mm Hg and therefore does not meet the criteria for septic shock (Answer C is incorrect). In the new sepsis definition, severe sepsis and systemic inflammatory response syndrome are no longer clinical entities in the spectrum of sepsis severity and should not be used (Answers A and D are incorrect).

7. **Answer: A**

The patient currently has a MAP less than 65 mm Hg and signs of a global lack of perfusion with an increased lactate concentration. Vasopressor therapy is indicated to sustain perfusion. This patient has underlying severe congestive heart failure with an ejection fraction of 20%; however, the $Scvo_2$ shows that the patient's Do_2 is sufficient, which suggests he is in distributive septic shock as opposed to cardiogenic shock. The SSC guidelines recommend initiating vasopressor therapy to target a MAP of 65 mm Hg and norepinephrine as the first-choice vasopressor (Answer A is correct). Vasopressin is currently recommended only as a secondary vasopressor, as an addition to catecholamine therapy (Answer B is incorrect). In septic shock, dobutamine is recommended only when the $Scvo_2$ is less than 70% and the patient has an adequate Hgb concentration (Answer C is incorrect). Epinephrine is currently recommended as an alternative to norepinephrine. In a study that compared epinephrine with norepinephrine plus dobutamine, the two arms did not differ in mortality outcomes; however, epinephrine was associated with lower pH values and higher lactate concentrations on day 1 (Answer D is incorrect).

8. **Answer: D**

According to the SSC guidelines, corticosteroids may be considered if patients have a poor response to fluid resuscitation and vasopressor therapy. In addition, guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine suggest corticosteroids only in patients requiring moderate- to high-dose vasopressors. In this case, the patient is receiving relatively low doses of vasopressors with an adequate MAP; hence, no steroids are currently necessary (Answer D is correct; Answers A and B are incorrect). Hydrocortisone is recommended at a dose of 200–400 mg/day. Administering it as a continuous infusion could be considered because this might lead to fewer variations in serum glucose. The ACTH stimulation test to determine which patients with sepsis should receive hydrocortisone is no longer recommended because the CORTICUS study showed that the ACTH stimulation test did not predict response to hydrocortisone therapy (Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

This older adult patient presents with septic shock. Shock is a syndrome of impaired Do_2, leading to tissue injury and end-organ failure. In this case, it is important to realize that fever is a symptom of an inflammatory syndrome, not a shock syndrome (Answers A, B, and D are incorrect). This patient's presentation with hypotension, confusion, and hyperlactatemia suggests the presence of a shock syndrome in the setting of impaired Do_2 (Answer C is correct).

2. **Answer: B**

The Fick equation for Do_2 best shows Do_2. According to this equation, Do_2 depends on CO and Cao_2. Cardiac output depends on heart rate and SV. Typically, an elevated heart rate will increase CO and Do_2. However, if a patient has atrial fibrillation, ventricular filling is impaired and SV is decreased, causing a decrease in CO and Do_2 (Answer B is correct). Lactate does not impede Do_2 but is a byproduct of impaired Do_2 (Answer A is incorrect). Similarly, Do_2 is not impaired by acute kidney injury (Answer C is incorrect). Finally, fever is an inflammatory response that increases Vo_2 but does not impair Do_2 (Answer D is incorrect).

3. **Answer: D**

The patient's laboratory values and arterial pH are consistent with hyperchloremic metabolic acidosis, and chloride-rich fluids should be avoided. Lactated Ringer's solution is considered a relatively chloride-poor solution (chloride content 111 mEq/L) and is best in this case (Answer D is correct). With its chloride content of 154 mEq/L, 0.9% sodium chloride is considered a chloride-rich fluid. Liberal use of chloride-rich fluids such as 0.9% sodium chloride has been associated with an increased need for renal replacement therapy (Answer A is incorrect). Although albumin 5% is considered a chloride-poor solution, data from randomized controlled trials have not supported a mortality benefit with albumin over crystalloids, even in the setting of hypoalbuminemia. Moreover, the patient has not received a "substantial volume" of crystalloids (she has received less than 30 mL/kg of fluid) that would coincide with recommendations to give albumin (Answer B is incorrect). Hydroxyethyl starch solutions may also have a high chloride content (depending on the formulation) and have been associated with an increased need for renal replacement therapy in the general critical care population, with no mortality benefit. Hydroxyethyl starch solutions should be avoided for fluid resuscitation in the ICU (Answer C is incorrect).

4. **Answer: B**

The patient has evidence of end-organ hypoperfusion (urinary output less than 0.5 mL/kg/hour and elevated lactate concentration without significant clearance), despite a MAP greater than 65 mm Hg and quantitative resuscitation. The patient probably needs a higher perfusion pressure because of a right-shifted zone of autoregulation secondary to hypertension. The norepinephrine dose should be increased to target a higher MAP; the exact target will depend on the patient's response and should be selected as the threshold that improves end-organ perfusion (Answer B is correct). The patient has no evidence of impaired CO (his $Scvo_2$ is not low); therefore, fluids (to improve SV) and inotropes (e.g., dobutamine) are not indicated (Answers C and D are incorrect). Because the patient has continued evidence of hypoperfusion, action should be taken, and the current therapy should be modified (Answer A is incorrect).

5. **Answer: B**

The patient has hypotension and signs of hypoperfusion with an elevated lactate concentration; possible interventions such as fluid administration should be explored further. Because the patient requires a high Fio_2, a reliable predictor of fluid responsiveness should be used to guide fluid therapy instead of administering fluid without respect to predicting responsiveness. In the setting of atrial fibrillation, an elevated PPV is not a reliable predictor of fluid responsiveness, and further evaluation should be done before fluids are administered (Answer A is incorrect). A PLR test can be used in both spontaneously breathing patients and those receiving mechanical ventilation to predict fluid responsiveness, and the patient has a method to assess the presence (or absence) of a CO response (Answer B is correct). Although the accuracy of the CO value from arterial pulse pressure waveform analysis may be somewhat limited by atrial fibrillation, this may be accounted for with the internal software of most devices and can be used to gauge a response to the PLR test. The patient has a femoral central venous catheter, which cannot be used to assess hemodynamic markers such as CVP or $Scvo_2$ (Answers C and D are incorrect). Furthermore, CVP is an inadequate predictor of fluid responsiveness.

6. **Answer: D**

The patient has features of vasodilatory shock secondary to an immune-mediated (“anaphylactic”) reaction (low preload, a low Scvo$_2$ [suggestive of poor Do$_2$], and an elevated lactate concentration). The patient should receive aggressive fluid resuscitation and be initiated on a vasopressor such as norepinephrine with the primary effects of augmenting afterload (Answer D is correct). Although the patient has features of poor Do$_2$, this is likely because of inadequate preload, which will be augmented by fluid administration. Agents targeted toward improving Cao$_2$ (PRBCs) and CO (dobutamine and milrinone) should not be initiated unless the patient has inadequate Do$_2$ and is not fluid responsive (Answers A–C are incorrect).

7. **Answer: A**

The patient has received an initial fluid challenge of only 23 mL/kg of crystalloids and still has evidence of end-organ hypoperfusion (elevated lactate concentration and urinary output less than 0.5 mL/kg/hour). An additional bolus of at least 500 mL of 0.9% sodium chloride is indicated to ensure an initial fluid challenge of at least 30 mL/kg of crystalloids and to improve end-organ perfusion (Answer A is correct). Because the patient has not received a complete initial fluid challenge (or even a substantial amount of crystalloids), albumin is not indicated (Answer B is incorrect). Vasopressors are not indicated right now because the patient’s MAP is above 65 mm Hg (the patient’s MAP is 67 mm Hg). In addition, if an initial vasopressor were to be selected, norepinephrine would be preferred (Answer C is incorrect). The patient’s low Scvo$_2$ is likely caused by inadequate preload (resulting in inadequate SV and CO). Adequate preload should be ensured before giving PRBCs as part of improving Do$_2$ (Answer D is incorrect).

8. **Answer: A**

Despite an initial fluid challenge of greater than 30 mL/kg of crystalloids, the patient has continued evidence of hypotension (MAP 63 mm Hg) and hypoperfusion (an elevated lactate and a urinary output less than 0.5 mL/kg/hour). A vasopressor should be initiated to improve blood pressure (MAP greater than 65 mm Hg) and organ perfusion. Norepinephrine is recommended by the SSC as the first-line vasopressor (Answer A is correct). Vasopressin is not recommended as the single initial vasopressor, but it may be added to norepinephrine (Answer B is incorrect). Phenylephrine is no longer recommended in the SSC guidelines. Although this patient has a history of atrial fibrillation and a high heart rate, norepinephrine should still be tried and the patient observed for signs of worsening tachyarrhythmias (Answer C is incorrect). Dopamine is recommended as an alternative vasopressor to norepinephrine in select patients, such as those with bradycardia. In a meta-analysis of patients with septic shock, dopamine was associated with a higher mortality rate and more frequent tachyarrhythmias (Answer D is incorrect).

9. **Answer: B**

Vasopressin can be added to norepinephrine to either increase MAP or lower norepinephrine requirements. In the VASST (Vasopressin and Septic Shock Trial) study comparing norepinephrine monotherapy with norepinephrine plus vasopressin, mortality did not differ between the two groups, but norepinephrine requirements were significantly lower in the patients allocated to receive AVP. According to the SSC guidelines, vasopressin can be added to norepinephrine to either raise the MAP or decrease the norepinephrine dosage (Answer B is correct). Although a dynamic marker of fluid responsiveness is not presented, the patient’s CO and cardiac preload are likely adequate, given that his Scvo$_2$ is 72%. Additional fluid loading is not indicated, given the information presented (Answer A is incorrect). Phenylephrine is no longer recommended as a treatment in the SSC guidelines; however, it has theoretical benefit as a second-line vasopressor when a malignant tachyarrhythmia is associated with norepinephrine. In this case, phenylephrine is not indicated because sinus tachycardia is not considered a malignant tachyarrhythmia (Answer C is incorrect). Epinephrine is recommended when an additional agent is needed to raise the MAP to the target. Adding epinephrine to norepinephrine would only add inotropic support, but this patient has no signs of low CO with an Scvo$_2$ of 72%, and the patient’s inadequate blood pressure is the most likely reason for his hypoperfusion (elevated lactate and low urinary output). Adding epinephrine would also likely increase the patient’s heart rate and potential for a tachyarrhythmia. As such, epinephrine is not indicated (Answer D is incorrect).

SHOCK SYNDROMES II

MAHMOUD A. AMMAR, PHARM.D., MBA, FCCM, BCCCP, BCPS

YALE NEW HAVEN HOSPITAL
NEW HAVEN, CONNECTICUT

SHOCK SYNDROMES II

Mahmoud A. Ammar, Pharm.D., MBA, FCCM, BCCCP, BCPS

Yale New Haven Hospital
New Haven, Connecticut

Learning Objectives

1. Identify critical determinants affecting oxygen delivery and the physiologic response to hypovolemic and obstructive shock.
2. Evaluate resuscitation strategies and end points in the management of hypovolemic, hemorrhagic, and obstructive shock.
3. Devise a treatment strategy for pharmacotherapy adjuncts in the management of bleeding and acute coagulopathy when treating patients with hemorrhagic shock.
4. Develop a treatment pathway for the care of patients receiving anticoagulants and antiplatelet agents for a life-threatening hemorrhage or critical bleeding that incorporates current evidence and guideline recommendations.
5. Apply risk stratification to guide the effective and safe use of thrombolytic agents in the management of acute pulmonary embolism.

Abbreviations in This Chapter

4F-PCC	4-factor prothrombin complex concentrate
ABC	Assessment of Blood Consumption
ACC	American College of Cardiology
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
CDT	Catheter-directed thrombolysis
CO	Cardiac output
DCR	Damage control resuscitation
DOAC	Direct oral anticoagulant
Do_2	Oxygen delivery
FAST	Focused Assessment with Sonography in Trauma
Fio_2	Fraction of inspired oxygen
GCS	Glasgow Coma Scale (score)
IVIG	Intravenous immunoglobulin
LV	Left ventricular
MTP	Massive transfusion protocol
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
PEA	Pulseless electrical activity
PH	Pulmonary hypertension
PRBC	Packed red blood cell
PT	Prothrombin time
rFVIIa	Recombinant activated factor VII
RV	Right ventricular
SJS	Stevens-Johnson syndrome
TBSA	Total body surface area
TEG	Thromboelastogram
TEN	Toxic epidermal necrolysis
TTE	Transthoracic echocardiogram

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 41-year-old man presents to the emergency department (ED) after a motorcycle accident. While the patient is being evaluated, it is apparent that he has broken ribs, a broken pelvis, and bilateral broken femurs. He is confused, and his vital signs are as follows: blood pressure 82/48 mm Hg, heart rate 125 beats/minute, respiratory rate 34 breaths/minute, and temperature 95°F (35°C). On further assessment, laboratory tests show that the patient has lost around 35% of his total blood volume. Which classification of hemorrhage from trauma most accurately describes this patient's condition?
   A. I.
   B. II.
   C. III.
   D. IV.

2. A 62-year-old man with a history of alcoholic cirrhosis and portal hypertension presents to the ED with weakness and hematemesis. Pertinent vital signs on admission are as follows: blood pressure 76/42 mm Hg, heart rate 134 beats/minute with a rhythm of sinus tachycardia, and respiratory rate 24 breaths/minute. Frank red blood is noted on nasogastric lavage. On physical examination, the patient is confused, with cold and clammy extremities. Pertinent laboratory values are as follows: hemoglobin (Hgb) 5.5 g/dL, blood urea nitrogen (BUN) 56 mg/dL, serum creatinine (SCr) 1.8 mg/dL, international normalized ratio (INR) 2.6, total bilirubin 7.5 mg/dL, central venous oxygen saturation ($Scvo_2$) 58%, and lactate 2.7 mmol/L. In this patient, which variable would best explain reduced oxygen delivery (Do_2) and which associated clinical or biochemical sign would best indicate a shock syndrome?

A. Elevated INR and hematemesis.
B. Sinus tachycardia and elevated serum creatinine.
C. Low hemoglobin and cold and clammy extremities.
D. Low $Scvo_2$ and hyperlactatemia.

3. A 44-year-old man (weight 82 kg) presents to the ED after a motor vehicle collision at highway speeds. On primary survey, his King airway device is replaced for an endotracheal tube; his respiratory rate is 37 breaths/minute, systolic blood pressure (SBP) is 77 mm Hg, heart rate is 146 beats/minute, and Glasgow Coma Scale score is 3. In addition, he is noted to have a positive seatbelt sign. The Focused Assessment with Sonography in Trauma (FAST) examination is positive. He is taken to the operating room for an emergency exploratory laparotomy. Which best represents the most appropriate initial transfusion, resuscitation, and hemostasis strategy to achieve hemodynamic stability?
   A. Give 2 L of warmed lactated Ringer solution, followed by a 2-unit transfusion of erythrocytes.
   B. Administer 30 mL/kg of warmed lactated Ringer solution and a tranexamic acid 1-g bolus, followed by 1 g infused over 8 hours.
   C. Obtain and send an INR, activated partial thromboplastin time (aPTT), fibrinogen, and complete blood cell count to guide initial resuscitation.
   D. Initiate massive transfusion, giving erythrocytes and plasma in a 1:1 ratio plus a tranexamic acid 1-g bolus and 1 g infused over 8 hours.

4. H.S. is a 76-year-old man (weight 142 kg) with a history of several pulmonary embolisms (PEs) and associated chronic thromboembolic pulmonary hypertension (CTEPH) on warfarin who is admitted to the ED with weakness and hematemesis. Pertinent vital signs on admission are as follows: blood pressure 82/46 mm Hg, heart rate 121 beats/minute with a rhythm of sinus tachycardia, and respiratory rate 22 breaths/minute. Frank red blood is noted on nasogastric lavage. On physical examination, the patient is confused, with clammy extremities. Pertinent laboratory values are as follows: Hgb 5.2 g/dL, BUN 52 mg/dL, SCr 2 mg/dL, INR 9.2, and platelet count (Plt) 120,000/mm^3. Which is most effective to immediately reverse his coagulopathy secondary to warfarin?
   A. Phytonadione 10 mg orally once.
   B. 4-factor prothrombin complex concentrate (4F-PCC) 50 units/kg intravenously infused over 30 minutes.
   C. Fresh frozen plasma 15-mL/kg infusion once.
   D. Phytonadione 10-mg intravenous push once.

5. A 66-year-old man with a medical history of non–small cell lung cancer presents to the ED with new-onset shortness of breath. A chest computed tomography (CT) scan reveals a PE at the bifurcation of the right and left pulmonary arteries. The patient is initiated on parenteral anticoagulation and transferred to the medical intensive care unit (ICU). On ICU admission, he develops pulseless electrical activity (PEA). He is intubated and mechanically ventilated, with recovery of spontaneous circulation after one round of chest compressions and epinephrine 1 mg. Which is the next best step to evaluate and/or treat this patient's PE?
   A. Administer alteplase 100 mg infused over 2 hours.
   B. Check a troponin T concentration.
   C. Check a brain natriuretic peptide concentration.
   D. Obtain a transthoracic echocardiogram (TTE).

Questions 6–8 pertain to the following case.

R.M is a 78-year-old man with a history of alcoholic cirrhosis and portal hypertension who is in an urban, academic ICU after treatment of a variceal hemorrhage (now stable) and respiratory failure. Five days after admission, he develops hypoxemia (partial pressure oxygen saturation [Pao_2] 78%), requiring an increased fraction of inspired oxygen (Fio_2) on the ventilator. A chest computed tomography angiography (CTA) reveals several filling defects at the bifurcation of the main pulmonary artery, suggesting a "saddle" PE. His heart rate is 142 beats/minute with a rhythm of sinus tachycardia. His blood pressure is 97/62 mm Hg and current weight is 87 kg. R.M. has a TTE that reveals right ventricular (RV) hypokinesis and tricuspid regurgitation. His cardiac troponin I (0.6 ng/mL) and troponin T (0.2 ng/mL) are positive.

6. Which would best categorize R.M.'s PE?
   - A. High risk.
   - B. Intermediate-high risk.
   - C. Intermediate-low risk.
   - D. Low risk.

7. After initiating therapeutic heparin and monitoring, R.M.'s blood pressure is now maintained at 90/50 mm Hg, but his oxygenation continues to worsen, now requiring 80% FIO_2. The medical team has decided that the patient's potential benefit from thrombolytic therapy outweighs the potential risks. Which is the best approach for this patient's thrombolytic administration?
   - A. Alteplase 100 mg infused over 2 hours.
   - B. Catheter-directed thrombolysis (CDT).
   - C. Alteplase 50 mg infused over 2 hours.
   - D. Alteplase 0.5 mg/hour by a pulmonary artery catheter.

8. As you prepare to implement the previously chosen treatment strategy, R.M. experiences cardiac arrest with PEA. Which is the most appropriate intervention for managing R.M.'s PE in the ICU setting?
   - A. Give alteplase 50 mg intravenous push once.
   - B. Proceed to surgical embolectomy.
   - C. Give alteplase 100 mg over 2 hours.
   - D. Abort cardiopulmonary resuscitation.

9. K.A. is a 50-year-old man admitted to the neurocritical care unit because of a head trauma causing a subarachnoid hemorrhage. On ICU day 3, his blood pressure is 70/50 mm Hg, and he is mechanically ventilated. K.A. was resuscitated with a normal saline bolus, and norepinephrine was initiated. A TTE reveals RV dilation and tricuspid regurgitation, and a CT scan reveals a filling defect within the pulmonary arteries, dilatation of the right ventricle of the heart, and enlargement of the pulmonary artery. K.A.'s condition continues to worsen, and vasopressin is added for refractory shock. Which is the best approach for treatment of K.A.'s shock?
   - A. Place an inferior vena cava filter.
   - B. Administer alteplase 100 mg infused over 2 hours.
   - C. Administer alteplase 50 mg infused over 2 hours.
   - D. Consult for possible catheter-directed thrombolysis.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 2, 4, 6
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 2, 4–6, 8
    b. Task B: 1, 2, 6, 10, 13, 15, 16
    c. Task C: 1–4
3. Domain 3: Professional Practice
    a. Task A: 5
    b. Task B: 1, 7

    Systems and patient care problems:
    - Hypovolemic shock
    - Acute traumatic coagulopathy
    - Burn resuscitation
    - Antithrombotic reversal
    - Obstructive shock
    - Social determinants of health
    - Disaster recovery

I. HYPOVOLEMIC SHOCK

A. Etiology and Epidemiology
   1. Hypovolemic shock is a result of reduced intravascular volume (i.e., reduced preload), which, in turn, reduces stroke volume and cardiac output (CO), leading to inadequate tissue perfusion. Hypovolemic shock accounts for around 16% of all cases of shock requiring vasoactive medications.
   2. In the United States, the most common form of shock secondary to trauma is hypovolemic shock, and exsanguination is estimated to be the direct cause of around 50,000 deaths from trauma in the United States (Table 1).
      a. Responsible for up to 30%–40% of trauma-related mortality
      b. Leading cause of death in patients younger than 45; thus, burden to society is even larger
   3. Although commonly associated with trauma, hypovolemic shock can also occur in other clinical scenarios (e.g., heat stroke, acute gastrointestinal [GI] bleeding, surgical, obstetrics, pharmacologic toxicity, burns, pancreatitis, loss of extracellular fluid).
   4. A study examined the impact of race and insurance status on trauma mortality rates among patients 18–64 years of age with an Injury Severity Score of 9 or higher caused by blunt or penetrating trauma, using data from the National Trauma Data Bank from 2001 to 2005. Specifically, the study aimed to determine whether race and insurance status independently predicted outcome disparities after trauma. The crude mortality rates were 5.7%, 8.2%, and 9.1% for the White, African American, and Hispanic groups, respectively ($p<0.005$). Crude mortality by insurance status was statistically lower for patients with insurance (4.4%) than for patients without insurance (8.6%) ($p<0.005$). The study also found that African American and Hispanic patients with insurance had higher mortality rates than White patients with insurance, and this effect worsened for patients without insurance across groups.

Table 1. Estimated Hemorrhage-Related Deaths/yr and Years of Life Lost in the United States and Worldwide, According to the Cause of Hemorrhage

Cause of Hemorrhage	Death from Hemorrhage (%)[a]	U.S. Cases		Global Cases	
		No. of Deaths/yr	Years of Life Lost	No. of Deaths/yr	Years of Life Lost
Trauma	30	49,440	1,931,786	1,481,700	74,568,000
Abdominal aortic aneurysm	100	9988	65,273	191,700	2,881,760
Peptic ulcer disease	60	1860	38,597	141,000	3,903,600
Maternal disorder	23	138	7572	69,690	4,298,240

[a] Estimates of deaths from hemorrhage as a percentage of all deaths from the given diagnosis.

Modified from: Cannon JW. Hemorrhagic shock. N Engl J Med 2018;378:370-9.

B. Pathophysiology
   1. Hypovolemic shock can be categorized as hemorrhagic and nonhemorrhagic:
      a. Whole blood loss (hemorrhagic): Whole blood loss can be external or internal.
         i. External hemorrhage: Trauma, surgical procedures, or penetrating injuries resulting in visible blood loss
         ii. Internal hemorrhage: Blood loss into body compartments or cavities (eg, retroperitoneal space, chest cavity, or limb hematomas) that may not be immediately apparent

   b. Plasma loss (nonhemorrhagic): Loss of extracellular fluid (e.g., burns, pancreatitis, third spacing, peritonitis, vomiting, diarrhea)
2. The estimated blood volume for a patient weighing 70 kg is 5 L (75 mL/kg for men and 65 mL/kg for women). Hemorrhagic shock occurs when intravascular volume loss impairs Do_2, generally greater than 30% of total blood volume loss.
3. Clinical features of hypovolemic shock include hypotension, tachycardia, diaphoresis, altered mentation, and decreased urinary output. If hypovolemic shock is secondary to blood loss from trauma, physiologic variables may be used to estimate the extent of blood loss (Table 2).

Table 2. Classification of Trauma Hemorrhage[a]

	Class I	**Class II (mild)**	**Class III (moderate)**	**Class IV (severe)**
Blood volume loss (%)	< 15%	15%–30%	30%–40%	> 40%
Heart rate	↔	↔/↑	↑	↑/↑↑
Blood pressure	↔	↔	↔/↓	↓
Pulse pressure	↔	↓	↓	↓
Respiratory rate	↔	↔	↔/↑	↑
Urine output	↔	↔	↓	↓↓
Glasgow Coma Scale score	↔	↔	↓	↓
Base deficit	0 to -2 mEq/L	-2 to -6 mEq/L	-6 to -10 mEq/L	-10 mEq/L or less

[a] Classification system is only intended as a guide to initial therapy because the physiologic response to hemorrhage represents a continuum. Confounding factors that influence the physiologic response to hemorrhage include patient age, severity of injury, time from injury, prehospital interventions, and medications for chronic conditions. Therefore, it is not intended to wait for a patient to fit each precise physiologic classification before initiating volume resuscitation.

Information from: 10th Edition of the Advanced Trauma Life Support® (ATLS®) Student Course Manual. American College of Surgeons, 2018.

4. Physiologic response
   a. Compensatory responses occur by different mechanisms ultimately aiming to maintain systemic perfusion.
   b. Neural response is immediate, occurring within minutes.
      i. Sympathetic response: Activation of the low-pressure receptors within the right and left atria and high-pressure receptors within the aortic arch and carotid sinus lead to increased secretion of epinephrine and norepinephrine, resulting in increased heart rate, myocardial contractility, and arteriolar/venous tone. Blood flow is preserved to critical organs.
      ii. Parasympathetic response: Reduced vagal tone leads to increased heart rate. Often, tachycardia is the earliest sign of circulatory shock from acute blood loss.
   c. Intrinsic response compensates for acute blood loss within hours.
      i. Reduced capillary pressure leads to fluid redistribution from the interstitial space to the vascular compartment as albumin shifts into the plasma.
      ii. The transcapillary refill can recruit up to 1 L into the intravascular compartment.
   d. Humoral response is delayed, developing over hours to several days. After decreased renal perfusion, secretion of antidiuretic hormone, aldosterone, and renin increases sodium and intravascular volume retention to restore the interstitial deficit from the transcapillary refill.

C. Acute Traumatic Coagulopathy (ATC):

1. There is no consensus regarding values defining traumatic coagulopathy, and various definitions exist. However, it is commonly defined as an increase in standard plasma-based coagulation tests above normal limits not associated with antiplatelet or anticoagulation therapy (aPTT, prothrombin time [PT], and INR). These include PT greater than 18 seconds, INR greater than 1.5, aPTT greater than 60 seconds, or any of these values at a threshold of 1.5 times the laboratory reference value. The prevalence of prolonged PT is higher, but prolongation of the PTT is more specific. In a multicenter, observational study, an INR-based definition of acute coagulopathy (INR greater than 1.5) was significantly associated with death (odds ratio [OR] 1.88; $p<0.001$), venous thromboembolism (OR 1.73; $p<0.001$), and multiorgan failure (OR 1.38; $p=0.02$).
2. Present in 25%–35% of injured civilian trauma patients on arrival at the ED and associated with a 40%–70% mortality rate, which likely plays a significant role in preventable deaths caused by hemorrhage
3. Pathophysiology of ATC is multifactorial:
    a. Inadequate tissue perfusion as the result of hypovolemia
    b. Subsequent cell hypoxia, anaerobic respiration, and metabolic acidosis
    c. Thrombin–thrombomodulin-complex generation caused by the tissue injury and the activation of anticoagulant and fibrinolytic pathways
    d. Hyperfibrinolysis plays a central role in the initial coagulopathy.
    e. Severe systemic hypothermia is associated with decreases in the enzymatic activity of clotting factors.
    f. Coagulopathy, acidosis, and hypothermia—known as the “lethal triad”—exacerbate one another, rapidly leading to death if not reversed.
    g. The DISPARITY study investigated whether sex differences existed in Surviving Sepsis Campaign resuscitation bundle completion, completion of individual bundle elements, or sepsis mortality. The study aimed to identify potential disparities in ED care for patients with sepsis on the basis of sex. The study reported that women with coagulopathy (INR greater than 1.5) may have received less aggressive care than men. The study showed a specific association of coagulopathy with bundle noncompletion in women (but not men) with an adjusted odds ratio of 0.49 (95% CI, 0.25–0.94). However, the analysis of sex-specific factors in survival showed a trend toward an association between bundle completion and survival in women but not men.
4. Characterization of ATC

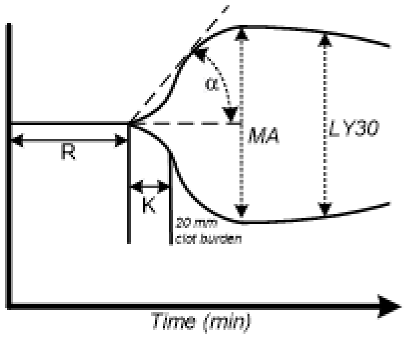


Figure 1. Features of a thromboelastogram.

α = α- angle; K = kinetics; LY30 = lysis at 30 minutes; MA = maximum amplitude; R = reaction time.

a. Standard coagulation laboratory or viscoelastic tests are recommended as monitoring techniques to characterize ATC (European Trauma Guidelines, grade 1C recommendation).

b. Viscoelastic tests play an emerging role in screening for coagulopathy in hemorrhagic shock.

   i. Whole blood coagulation tests that represent global clot function, including clot initiation, formation, stabilization, and fibrinolysis, correlate well with standard plasma coagulation studies and may be available as point-of-care tests with a faster turnaround time.

   ii. Available tests include thromboelastogram (TEG) and rotational thromboelastometry (ROTEM), which are more commonly used in the United States and Europe, respectively.

   iii. TEG outputs include a graphic representation of clot kinetics (Figure 1 and Figure 2).

   iv. Retrospective studies show that TEG-guided resuscitation in trauma patients reduces mortality, decreases blood product use, and helps identify hyperfibrinolysis. The ITACTIC randomized controlled trial, involving 396 trauma patients under a massive transfusion protocol (MTP), found no significant difference in the primary end point of days alive and free from MTP at 24 hours when comparing TEG (201 patients) with conventional tests (195 patients). Many participants did not require extensive transfusions or meet the criteria for trauma-induced coagulopathy, potentially influencing the study's outcomes. However, a trend toward improved mortality was observed in patients receiving TEG-guided care experiencing coagulopathy, and in those with traumatic brain injury, the group receiving TEG-guided care had statistically more days alive without MTP activation. Another smaller randomized controlled trial involving 111 trauma patients showed a higher 28-day survival rate (80.3% vs 63.6%) and reduced use of plasma or platelets in the group receiving TEG-guided care compared with conventional testing. This difference was apparent within the first 6 hours after trauma, suggesting that early hemostasis guided by TEG improves survival. Although smaller than the ITACTIC trial, this study supports a role for TEG-guided care in the treatment of trauma patients.

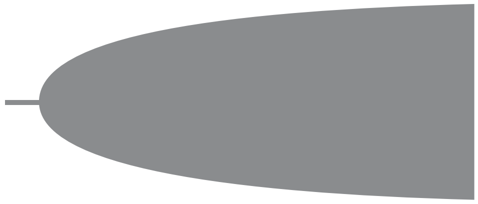
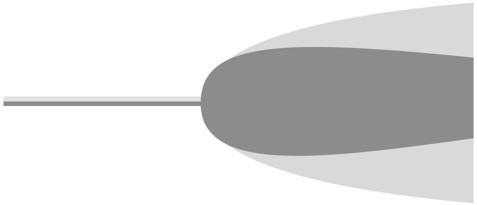
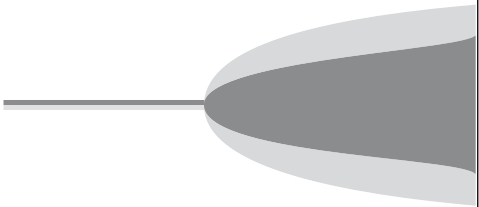
TEG Tracing	Interpretation	Treatment
	Hypercoagulable	Enoxaparin or heparin prophylaxis when possible
	Hyperfibrinolysis	Tranexamic acid
	Fibrinogen deficiency	Cryoprecipitate -or- Concentrated fibrinogen

Figure 2. Examples of TEG tracings (dark) relative to the control (light) with corresponding interpretation and treatments.

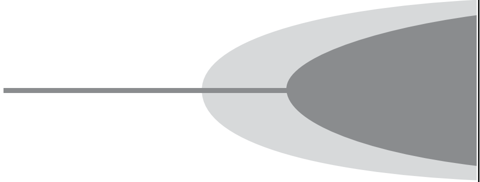
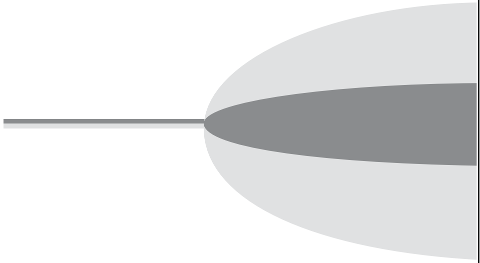
TEG Tracing	Characterize	Treatment
	Factor deficiency	Plasma -or- prothrombin complex concentrate
	Platelet dysfunction	Platelet transfusions -or- desmopressin

Figure 2. Examples of TEG tracings (dark) relative to the control (light) with corresponding interpretation and treatments. (*Con't*)

Table 3. TEG Output Parameters and Normal Values

TEG Parameters	Description	Normal Range[a] (kaolin-activated)	Treatment
Reaction (R) time	Time until evidence of a first clot is detected. Time of latency from start to initial fibrin formation because of effects of factor VIIa and tissue factor (time until fibrin clot formation)	3–9 min	Fresh frozen plasma if elevated
Kinetics (K)	Time from the end of R (factor initiation and start of clot formation) until the clot reaches 20 mm amplitude of clot strength (speed of clot formation), which represents platelet activity, factor levels, and fibrinogen	1–3 min	Cryoprecipitate if elevated
α-Angle	The speed at which fibrin buildup and cross-linking take place (clot strengthening) and hence assesses the rate of clot formation	55–78 degrees	Cryoprecipitate if decreased
Maximum amplitude (MA)	Represents the strongest point of fibrin clot, predominantly platelets but also fibrinogen (80% of the MA is derived from platelet function, and the remaining 20% is derived from fibrin)	51–69 mm	Platelets if decreased
Estimated percent lysis or lysis at 30 min (LY30)	Represents the percent decrease in amplitude 30 min after MA and measures the degree of fibrinolysis	0%–8%	Aminocaproic acid if increased

[a] Standard TEG is kaolin-activated, and values differ if native blood is used. TEG using native whole blood is slower (R-time 4–8 min, α-angle 47–74 degrees, MA 55–73 mm, K 1–4 min, and LY30 typically not reported or interpreted).

TEG = thromboelastography.

Information from: Gonzalez E, Pieracci FM, Moore EE, et al. Coagulation abnormalities in the trauma patient: the role of point-of-care thromboelastography. Semin Thromb Hemost 2010;36:723-37.

D. Coagulopathy of Chronic Liver Disease
   1. Patients with chronic liver disease often have episodes of clinically meaningful bleeding events confounded by decreased concentrations of most endogenous procoagulant factors, except for factor VIII and von Willebrand factor.
   2. Historically, the basic laboratory tests of coagulation (e.g., PT, aPTT) have been used to determine the risk of bleeding, despite their poor correlation with onset and duration of bleeding after liver biopsy or predicting the occurrence of GI hemorrhage.
   3. This is likely explained by the parallel reduction in endogenous anticoagulants (e.g., antithrombin, protein C) in chronic liver disease, leading to a “balanced state of coagulation.”
   4. Randomized controlled trials evaluating recombinant activated factor VII (rFVIIa) to reverse the coagulopathy of chronic liver disease showed dramatically improved PT, but rFVIIa failed to alter bleeding complications during liver transplantation or control bleeding in variceal hemorrhage.
   5. The American Association for the Study of Liver Diseases (AASLD) 2017 updated guideline for managing portal hypertensive bleeding in cirrhosis recommends against the use of fresh frozen plasma or rFVIIa to correct an INR because INR is not a reliable indicator of coagulation in cirrhosis, and evidence is lacking that this improves outcomes. In addition, the American Gastroenterological Association (AGA) 2021 guidelines on coagulation in cirrhosis state that the balanced nature of alterations in hemostasis associated with end-stage liver disease is complex and that an elevated INR is not necessarily predictive of bleeding outcomes in patients with cirrhosis. For patients with stable cirrhosis (with known baseline abnormal coagulation parameters) undergoing common GI procedures, the AGA suggests against the use of extensive preprocedural testing (including repeated measurements of PT/INR or Plt) and against the routine use of blood products (e.g., fresh frozen plasma and Plt) for bleeding prophylaxis.
   6. Global clotting tests (e.g., the thrombin generation test or TEG) have the potential to characterize coagulopathy in chronic liver disease but may not be routinely available, and optimal transfusion thresholds remain undefined.

E. Resuscitation
   1. Rapid identification and correction of the source of bleeding is the definitive treatment (e.g., surgical exploration, angiographic embolization, stabilization of the pelvic ring, damage control surgery).
   2. Fluids
      a. Indications: Diminished mental status or absent radial pulse (SBP less than 90 mm Hg)
      b. Benefits: Fluids restore intravascular volume, reverse tissue hypoperfusion, and correct oxygen deficit.
      c. Risks: Fluids do not increase oxygen-carrying capacity, can precipitate dilutional coagulopathy, and lead to interstitial fluid accumulation, including the development of pulmonary edema and worsening acute respiratory distress syndrome.
      d. Isotonic saline is indeed commonly used, and there is evidence that its high chloride content can lead to hyperchloremic metabolic acidosis. This has been linked to adverse renal effects, including an increased risk of acute kidney injury in some studies. However, not all studies have shown a definitive causal relationship between saline use and acute kidney injury. The strength of this association may depend on the context (eg, volume administered, patient population). Evidence of their effect on mortality and morbidity is still emerging.
      e. Colloids: Confer no incremental benefit over crystalloids, were associated with increased mortality in a subgroup analysis of patients with severe brain injury in the SAFE trial, likely secondary to hypo-osmolarity. Synthetic colloids (e.g., hydroxyethyl starches) contribute to coagulopathy and the risk of acute kidney injury and should therefore be avoided.

    f. Recommendations: Isotonic crystalloids are indicated in hemorrhagic shock. In trauma, restricted volume replacement, usually less than 1.5 L of a balanced crystalloid, should be used initially, and hypotonic solutions (e.g., lactated Ringer with a sodium content of 131 mmol/L) should be avoided in patients with head trauma to minimize fluid shifts into the cerebral tissue. The most recent European guidelines on managing major bleeding and coagulopathy after trauma recommend isotonic balanced crystalloids over saline.

3. Packed red blood cells (PRBCs) and blood products
    a. Indicated when the estimated blood loss is greater than 30% of the total blood volume. Each PRBC unit is expected to increase circulating Hgb by around 1 g/dL.
    b. Amount of blood products to transfuse is based on clinical examination, given that the initial hemoglobin or hematocrit reading may not reflect blood loss because of compensatory mechanisms.
    c. Although there are no randomized controlled trials evaluating transfusion thresholds for trauma, the European guidelines on managing major bleeding and coagulopathy after trauma recommend maintaining a hemoglobin of 7–9 g/dL after initial resuscitation.
    d. In acute upper GI bleeding, a restrictive transfusion threshold (Hgb less than 7 g/dL) compared with a liberal transfusion threshold (Hgb less than 9 g/dL) was associated with a higher 6-week survival rate (95% vs. 91%, hazard ratio [HR] 0.55 [95% confidence interval [CI], 0.33–0.92; p=0.02]) and lower rates of further bleeding (10% vs. 16%, p=0.01) and adverse effects (40% vs. 48%, p=0.02).
        i. Notable limitations of the study include its single-center design and exclusion of patients with cirrhosis who have cardiovascular disease.
        ii. Despite these limitations, a transfusion threshold of 7 g/dL was endorsed by the 2017 AASLD Practice Guidance for Portal Hypertension Bleeding in Cirrhosis, with recommendations to maintain hemoglobin at 7–9 g/dL.
    e. A randomized controlled trial of patients undergoing cardiac surgery compared a restrictive transfusion threshold (less than 7.5 g/dL) with a liberal transfusion threshold (less than 9 g/dL).
        i. The groups did not differ with respect to the composite primary end point of serious infection or ischemic event (35.1% vs. 33.0%; OR 1.11; 95% CI, 0.91–1.34; p=0.30).
        ii. However, more deaths occurred in the restrictive transfusion group (4.2% vs. 2.6%; HR 1.64; 95% CI, 1.00–2.67; p=0.045).
        iii. Therefore, a restrictive transfusion strategy after cardiac surgery cannot be recommended.
    f. A study examined transfusion practices in hospitalized general medicine patients and tested for differences in the Hgb concentration at which patients have transfusions and the total number of RBC units received by patients' race. The study aimed to determine any disparities in transfusion practices according to race. In this study, African Americans had lower transfusion rates than Whites (25% vs. 30%, respectively; p<0.01). For Hgb concentrations below a nadir Hgb of 9 g/dL, African Americans had significantly lower transfusion rates than Whites. The transfusion rate for Hgb concentrations of 8.0–8.9 g/dL was 1% for African American patients versus 7% for White patient (p<0.01). The transfusion rate for Hgb concentrations of 7.0–7.9 g/dL was 15% and 28% for African Americans and Whites, respectively (p<0.01). The transfusion rate for Hgb concentrations below 7 g/dL was 80% for African Americans versus 86% for Whites (p<0.01). African American patients also received fewer units of RBCs overall, with a beta coefficient of -0.17 (p<0.01), and at lower Hgb concentrations, with a beta coefficient of 0.14 (p<0.01), than White patients. These observed differences in the receipt of transfusion by race met the definition of a health care disparity.

4. Vasopressors
    a. Attractive adjuncts in hemorrhagic shock to minimize the amount of fluid required to reverse tissue hypoperfusion, but can increase cardiac afterload and are independently associated with increased mortality in trauma

b. Similar to other shock states, a relative arginine vasopressin deficiency develops in hemorrhagic shock that is associated with catecholamine resistance, vasoplegia, and increased venous capacitance. Supplemental vasopressin may be an adjunct to blood product resuscitation in hemorrhagic shock.
   i. The AVERT-Shock trial was a single-center, randomized controlled trial investigating the impact of low dose vasopressin (up to 0.04 units/min), compared to placebo, in adult trauma patients who required at least 6 units of any blood product within 12 hours of injury. They found that patients who received vasopressin required significantly less cumulative volume of all blood products by around 1 L, and had a decreased incidence of deep vein thrombosis. No difference was noted in other complications, such as acute respiratory distress syndrome, or outcomes, including mortality.
   ii. Although this study challenges the traditional practice of avoiding vasopressors in a bleeding trauma patient, confirmatory research is needed to determine if vasopressin significantly improves morbidity and mortality.

c. In life-threatening hypotension, vasopressors may be recommended only after hypovolemia has been corrected or when cardiac arrest is imminent.

5. End points of resuscitation
   a. General recommendations include permissive hypotension, defined as SBP 80–90 mm Hg for most patients, and urinary output greater than 30 mL/hour. Up to 85% of patients may be under-resuscitated using SBP and urinary output as end points.
   b. In patients with traumatic brain injury, permissive hypotension should be avoided. The 2016 Brain Trauma Foundation guidelines recommend maintaining SBP at 110 mm Hg or greater for patients 15–49 years of age or older than 70 and at 100 mm Hg or greater in patients 50–69 years of age.

Patient Case

1. A 67-year-old man is accidentally shot in the buttocks while deer hunting with his friends. He is brought to the ED immediately. While in transfer, the patient receives 500 mL of lactated Ringer solution. His vital signs on admission to the ED are as follows: blood pressure 104/58 mm Hg, heart rate 108 beats/minute, respiratory rate 22 breaths/minute, and temperature 95°F (35°C). On examination, he has 8/10 pain and appears anxious. Which is best for resuscitation strategies?
   A. Administer lactated Ringer solution at 1000 mL/hour to maintain a urinary output greater than 30 mL/hour and an SBP greater than 100 mm Hg.
   B. Transfuse 2 units of PRBCs and administer a 1-L bolus of lactated Ringer solution to maintain a urinary output greater than 1 mL/kg/hour.
   C. Transfuse 2 units of PRBCs, 2 units of fresh frozen plasma, and a 1-L bolus of lactated Ringer solution to normal mentation.
   D. Administer lactated Ringer solution at 1000 mL/hour to maintain a urinary output greater than 30 mL/hour, an SBP greater than 80–90 mm Hg, and normal mentation.

F. Burn Resuscitation
   1. Acute thermal injury triggers an inflammatory state that ultimately leads to third spacing of intravascular fluid.
   2. Fluid resuscitation is initiated to maintain perfusion to tissue beds and end-organ function. A concomitant concern is to avoid over-administration of fluids, leading to abdominal or extremity compartment syndrome, acute respiratory distress syndrome, and further third spacing.

3. The 2008 American Burn Association (ABA) practice guidelines for burn shock resuscitation promote fluid resuscitation to target a urine output of 0.5–1 mL/kg/hour in adults, with the initial rate determined by the total body surface area (TBSA) burned and body weight. Given a lack of strong evidence, the ABA recommends against a preload-driven resuscitation target from an invasive monitor unless special circumstances exist (e.g., older patients or inadequate response to treatment).
4. Many formulas exist to estimate crystalloid need, but the most common strategy is administering crystalloid fluid using lactated Ringer solution by the Parkland formula: 4 mL x kg x % TBSA, with half administered over the first 8 hours from the time of the burn injury and the remaining half over the next 16 hours.
5. In practice, significantly more fluid is often given to burn patients than is predicted by traditional formulas.
    a. While maintaining a urinary output more than 0.5 mL/kg/hour, the average patient with a severe burn receives around 6 mL/kg/% body surface area within the first 24 hours, leading to the potential for "fluid creep" and associated complications of over-resuscitation.
    b. Therefore, some formulas now advocate less initial fluid, such as the "modified" Brooke formula (2 mL/kg/% body surface area).
    c. The U.S. Army Institute of Surgical Research (USAISR) rule of 10 (% TBSA burn x 10 = initial rate) is a simplified equation that determines the initial starting rate for fluid resuscitation, and subsequent rate changes are guided by maintaining a urinary output greater than 0.5 mL/kg/hour.
6. Burn resuscitation formulas serve as an initial starting dose, and ongoing resuscitation should be individualized.
7. Difficult to resuscitate: When a patient's fluid requirement exceeds what is expected according to the traditional formulas, albumin may be added. When added, the current fluid rate is maintained, but albumin replaces 33%–66% of the total rate. High dose ascorbic acid (e.g., 66 mg/kg/hr) has been shown to decrease total fluid requirements, but guidelines state more evidence is needed before this therapy can be recommended routinely.

Patient Case

2. A 29-year-old man (height 72 inches, weight 85 kg) is admitted to the burn unit with a 40% TBSA burn to the lower extremities and buttocks after a fall into a molten slag at work in a steel mill. He received 500 mL of normal saline during transfer to the hospital. On his presentation to the burn unit, the surgical resident asks for your help in calculating the patient's fluid resuscitation needs. Which is best for resuscitation?
    A. 15 L of lactated Ringer solution over 24 hours; initiate at 1000 mL/hour for the first 12 hours, followed by 250 mL/hour, titrating to goal urinary output of 1 mL/kg/hour.
    B. 13 L of lactated Ringer solution over 24 hours; initiate at 813 mL/hour for the first 8 hours, followed by 406 mL/hour, titrating to goal urinary output of 0.5 mL/kg/hour.
    C. 12 L of lactated Ringer solution over 12 hours; initiate at 1000 mL/hour, titrating to goal urinary output of 0.5 mL/kg/hour.
    D. 24 L of lactated Ringer solution over the first 24 hours; initiate at 1000 mL/hour, titrating to goal urinary output of 0.5 mL/kg/hour.

G. Blood Product Resuscitation
1. Lethal triad: Hypothermia, acidosis, and coagulopathy
    a. Hypothermia, severe acidemia (pH less than 7.20), and hypocalcemia inhibit the procoagulant enzyme function.

   b. Therefore, treatment of the acutely bleeding patient should prioritize warming the patient to a temperature greater than 93.2°F (34°C), correcting acidosis to a pH greater than 7.20, and administering calcium to an ionized calcium greater than 4.4 mg/dL (1.1 mmol/L).
2. Damage control resuscitation (DCR) is a comprehensive approach in trauma care that integrates permissive hypotension, hemostatic resuscitation, and damage control surgery to address the lethal triad of coagulopathy, acidosis, and hypothermia. Key components of DCR include:
   a. Permissive hypotension: Maintaining lower blood pressure to minimize bleeding while ensuring vital organ perfusion
   b. Hemostatic resuscitation: Administering blood products in balanced ratios to support clotting and prevent dilutional coagulopathy
   c. Damage control surgery: Performing rapid, initial surgical interventions to control bleeding and contamination, deferring definitive repairs until the patient's condition stabilizes
3. Initial bleeding and coagulopathy should be managed with blood component therapy (e.g., plasma, platelets, cryoprecipitate) to build whole blood.
   a. Standard MTPs include at least a 1:1:1 strategy of PRBCs/plasma/platelets.
   b. The multicenter, randomized PROPPR trial compared a balanced 1:1:1 DCR transfusion strategy of plasma/platelets/PRBCs with a ratio of 1:1:2 in adult trauma patients.
      i. 1:1:1 group received 6 units of plasma, one dose of platelets (6 units of platelets), and 6 units of PRBCs. Transfusion order was platelets first, followed by alternating plasma and PRBC units.
      ii. 1:1:2 group received an initial container (and all subsequent odd-numbered containers) with 3 units of plasma, no doses of platelets, and 6 units of PRBCs. The second (and all subsequent even-numbered containers) had 3 units of plasma, one dose of platelets (6 units of platelets), and 6 units of PRBCs. Transfusion order was platelets first, followed by alternating 2 units of PRBCs and 1 unit of plasma.
      iii. 24-hour mortality (12.7% in 1:1:1 group vs. 17.0% in 1:1:2 group; adjusted RR 0.75; 95% CI, 0.52–1.08; p=0.12) and 30-day mortality (22.4% in 1:1:1 group vs. 26.1% in 1:1:2 group; adjusted RR 0.86; 95% CI, 0.65–1.12; p=0.26) did not differ significantly.
      iv. However, in the 1:1:1 arm, hemostasis was achieved in more patients (86.1% vs. 78.1%, p=0.006), possibly highlighting the importance of early platelet transfusion, and fewer experienced death caused by exsanguination (9.2% vs. 14.6%; p=0.03).
4. Application of DCR in the prehospital setting has been investigated to intervene as close to the time of injury as possible to prevent the development of coagulopathy, irreversible shock, and the ensuing inflammatory response.
   a. The Prehospital Air Medical Plasma (PAMPer) trial was designed to determine the efficacy and safety of prehospital administration of 2 units of plasma resuscitation with or without red blood cells compared with standard of care (crystalloids with or without red blood cells) in severely injured patients at risk of hemorrhagic shock.
      i. Patients were eligible if they had at least one episode of hypotension (SBP less than 90 mm Hg), tachycardia (heart rate greater than 108 beats/minute), or severe hypotension (SBP less than 70 mm Hg) in the prehospital setting.
      ii. 501 patients were enrolled, with a median prehospital transport time of 40–42 minutes.
      iii. After arrival at the trauma center, the PT ratio was lower in the plasma group (1.2 vs. 1.3; p<0.001). Mortality rates at 24 hours (13.9% vs. 22.1%; p=0.02) and 30 days (23.2% vs. 33%; p=0.03) were lower in the plasma group, with early separation in the Kaplan-Meier survival curve at 3 hours. There was no difference in inflammation-mediated complications, including multiorgan failure, acute respiratory distress syndrome, or nosocomial infections, nor did transfusion-related reactions differ, suggesting prehospital plasma is safe.

b. In contrast, the benefits of prehospital plasma may not be as apparent in an urban setting with short prehospital transport times. In a single-center study at Denver Health Medical Center, prehospital plasma failed to improve mortality at 28 days (15% plasma vs. 10% control; p=0.37) and was terminated early for futility after 144 enrollments.

c. Although logistical challenges are related to the storage and shelf life of plasma in a variety of preparations, trauma centers may consider implementing prehospital plasma for patients at risk of hemorrhagic shock, particularly in rural settings with longer transport times.

H. Massive Transfusion Protocol

1. Massive transfusion: defined as a transfusion of 10 units or more of RBCs in 24 hours, 3 units of RBCs over 1 hour, or any four blood components in 30 minutes
2. Focused Assessment with Sonography in Trauma (FAST) instrument can be used to evaluate trauma patients with suspected abdominal and thoracoabdominal injuries and detect hemorrhages in the peritoneal, pleural, and pericardial cavities.
3. Clinical scores have been developed to assist in early identification of patients who would benefit from activation of the MTP. The Assessment of Blood Consumption (ABC) Score was utilized in the PROPPR trial for study enrollment. Two or more of the following criteria are associated with high sensitivity and specificity for requiring an MTP: penetrating mechanism of injury, ED SBP 90 mm Hg or less, ED heart rate 120 beats/minute or greater, or a positive FAST examination.
4. Current recommendations for the initial management of an expected massive hemorrhage include PRBCs and plasma in a ratio of at least 2:1 as needed, or fibrinogen concentrate and PRBCs (European Trauma Guidelines 2019; grade 1C).
5. Further resuscitation, including platelet transfusions, should be guided in a goal-directed fashion, using either standard laboratory coagulation assays or viscoelastic tests (grade 1B). An example of goal-directed resuscitation can be found in Table 4.
6. In a prospective study of 111 patients, TEG-guided resuscitation was superior to standard laboratory coagulation-guided resuscitation with improved 6-hour mortality (7.1% vs. 21.8%; p=0.032) and total mortality (19.6% vs. 36.4%; p=0.049) and required less plasma and platelets in the first 2 hours of resuscitation. Notable limitations include single-center study design and TEG being available at point of care. This finding is supported by growing evidence for viscoelastic testing in trauma care, but adoption of TEG/ROTEM remains limited in some centers because of cost and resource constraints.

Table 4. Example of Goal-Directed Resuscitation

Conventional Coagulation Assay (CCA)	Thromboelastography (TEG)
INR ≥ 1.5: 2 units of FFP Fibrinogen < 150 mg/dL: 10 pack of cryoprecipitate Plt < 100,000/mm^3: 1 unit of apheresis platelets D-dimer > 0.5 mcg/mL: 1 g of tranexamic acid	Initial activated clotting time ≥ 140 s: 2 units of FFP, 10 pack of cryoprecipitate, 1 unit of apheresis platelets Activated clotting time > 111–139 s[a]: 2 units of FFP Alpha angle < 63: 10 pack of cryoprecipitate MA < 55 mm: 1 unit of apheresis platelets LY30[b] > 3%: 1 g of tranexamic acid

[a] Equivalent to R-time > 10

[b] LY30 is a reflection of fibrinolysis, similar to estimated percent lysis.

FFP = fresh frozen plasma; LY30 = percent decrease in amplitude after 30 minutes; MA = maximum amplitude; Plt = platelets.

Information from: Gonzalez E, Moore EE, Moore H, et al. Goal directed resuscitation of trauma induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assay. Ann Surg 2016;263:1051-9.

7. Some metabolic complications are associated with massive transfusions that are notable for pharmacotherapy considerations.
   a. Potassium abnormalities may include hypokalemia or hyperkalemia.
      i. Hyperkalemia:
         (a) ATPase pumps become deactivated in stored blood, leading to elevations in potassium concentrations from 7 mEq/L to 77 mEq/L.
         (b) After transfusion, the ATPase pump is restored, and potassium is shifted intracellularly.
         (c) Although this generally leads to minimal sequelae, hyperkalemia may develop in those with renal insufficiency or severe tissue injury and transfusion rates. Rapid transfusion through a central venous catheter has been associated with hyperkalemia-induced cardiac arrest.
         (d) For patients at risk, the recommended management is to slow the infusion rate to less than 100–150 mL/minute.
      ii. Hypokalemia: Secondary to restoration of the ATPase pump on transfusion, shifting potassium intracellularly, metabolic alkalosis from citrate administration, release of hormones (e.g., aldosterone, antidiuretic hormone), and co-infusion of potassium-poor solutions (e.g., normal saline)
      iii. Potassium should be closely monitored and managed during massive transfusion.
   b. Complications secondary to citrate:
      i. Each unit of stored blood is anticoagulated with around 3 g of citrate. The metabolic capacity of the liver for citrate metabolism is around 3 g every 5 minutes, which is diminished with underlying liver dysfunction or in shock states leading to citrate accumulation.
      ii. Accumulation of citrate after several transfusions may bind endogenous calcium, inducing severe hypocalcemia, prolonged QT intervals, circulatory depression, hypotension, tremors, and PEA.
      iii. Therefore, it is critically important to monitor ionized calcium concentrations and to administer calcium chloride or calcium gluconate to maintain normal concentrations.
      iv. Evidence is currently lacking regarding optimal calcium dosing in a massive transfusion. Calcium chloride 1–3 g is often the preferred dose and preparation in the setting of MTP due to the higher potency of elemental calcium relative to calcium gluconate. The total elemental calcium concentration in calcium chloride 10% and calcium gluconate 10% is 270 mg/10 mL and 90 mg/10 mL, respectively.
      v. Magnesium may also be bound by citrate, which can further increase the effects of hypocalcemia, necessitating appropriate monitoring and management.
      vi. Although citrate is metabolized to bicarbonate, which may induce metabolic alkalosis, with prolonged storage, PRBCs have a pH below 7.0, contributing to metabolic acidosis. Metabolic acidosis is more common in patients requiring a massive transfusion, given hypoperfusion and anaerobic metabolism in a shock state.

I. Antifibrinolytics
   1. Tranexamic acid
      a. An antifibrinolytic agent that binds plasminogen to prevent the dissolution of a fibrin clot. Tranexamic acid is a competitive inhibitor of plasmin and plasminogen.
      b. CRASH-2 trial:
         i. Evaluated the effects of tranexamic acid in adult trauma patients with, or at risk of, significant bleeding who were within 8 hours of injury compared with placebo (0.9% saline). Tranexamic acid (loading dose of 1 g over 10 minutes, followed by a 1-g infusion over 8 hours) reduced 28-day mortality for all-cause trauma compared with placebo (relative risk [RR] 0.91; 95% CI, 0.85–0.97; p=0.0035).

    - ii. The number needed to treat is 67, and no difference between groups was noted in the risk of vascular occlusive events.
    - iii. In a separately published exploratory analysis, the greatest benefit for tranexamic acid occurred with administration within 3 hours of injury (RR 0.68 1 hour or less from injury; 95% CI, 0.57–0.82; p<0.0001; RR 0.79 1–3 hours from injury; 95% CI, 0.64–0.97; p=0.03), with an increased risk of death from bleeding after 3 hours from injury (RR 1.44; 95% CI, 1.12–1.84; p=0.004).
    - iv. Major limitations of this trial were that few patients were enrolled from regions with modern trauma systems (e.g., blood product availability, MTP), and the baseline mortality was higher than expected in North America or Europe.
- c. CRASH-3 trial:
    - i. Evaluated the effects of tranexamic acid (same dosing regimen as used in CRASH-2) in patients with traumatic brain injury. Patients were enrolled within less than 3 hours of injury with either Glasgow Coma Scale (GCS) score less than 13 or intracranial hemorrhage on CT scan and no major extracranial bleeding.
    - ii. There was no difference in head injury–related death within 28 days with tranexamic acid (18.5%) compared with placebo (19.8%) (RR 0.94; 95% CI, 0.86–1.02).
    - iii. Tranexamic acid reduced death in patients with mild to moderate TBI, GCS 9–15 (RR 0.78; 95% CI, 0.64–0.95), but not in patients with a severe head injury, GCS 3–8 (RR 0.99; 95% CI, 0.91–1.07) who already had extensive intracranial hemorrhage before treatment.
    - iv. Patients in CRASH-3 were sicker than those in CRASH-2, with head injury–related death 12% in CRASH-2 versus 19% in CRASH-3.
- d. In the MATTERs (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation) study, tranexamic acid was associated with a 6.5% absolute reduction in in-hospital mortality for all patients. A 13.7% absolute reduction occurred in those requiring massive transfusion, suggesting a greater benefit in those with a higher severity of injury.
- e. In the MATTERs II trial, adding fibrinogen (cryoprecipitate) to tranexamic acid further improved in-hospital mortality compared with tranexamic acid alone (11.6% vs. 18.2%; p=0.03).
- f. In trauma, tranexamic acid has not been shown to decrease the need for transfusion.
- g. Recommendations related to tranexamic acid use in trauma:
    - i. When given, should be administered as early as possible to a trauma patient with bleeding or within 3 hours of injury to a patient at risk of significant hemorrhage. Administered as a loading dose of 1 g infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours
    - ii. Some hospital systems have begun giving the tranexamic acid loading dose prehospital to prevent full activation of fibrinolysis, with improved outcomes when the loading dose was given within 1 hour of injury. This strategy requires validation in a clinical trial.
    - iii. Additional safety concerns have been identified related to tranexamic acid in trauma patients.
        - (a) Although not shown in initial trials, tranexamic acid was subsequently associated with thrombotic events, including PE and venous thromboembolism (MATTERs trial).
        - (b) In addition, tranexamic acid may be associated with fibrinolysis shutdown, a state of suppressed fibrinolysis associated with high mortality from multiorgan failure.
    - iv. Because of criticisms of previous trials and potential safety concerns, some experts advocate the use of tranexamic acid only in select patients having a diagnosis of hyperfibrinolysis, but no study on selective use of tranexamic acid has shown improved outcomes.
    - v. In the United States, the Eastern Association for the Surgery of Trauma (EAST) guidelines for DCR conditionally recommended tranexamic acid as a hemostatic adjunct in severely injured trauma patients.

   h. Tranexamic acid in postpartum hemorrhage:
      i. In the WOMAN trial, a tranexamic acid 1-g bolus (which may be repeated at 30 minutes if bleeding persisted after the initial dose) did not affect all-cause mortality but did reduce mortality from postpartum hemorrhage if administered within 3 hours compared with placebo (1.2% vs. 1.7%; RR 0.69; 95% CI, 0.52–0.91; p=0.008).
      ii. The World Health Organization strongly recommends tranexamic acid within 3 hours for postpartum hemorrhage.
   i. The importance of early tranexamic acid was evaluated in an integrated analysis of both the WOMAN trial and the CRASH-2 trial. For every 15-minute delay to tranexamic acid, the overall benefit was decreased by around 10%, highlighting the importance of early administration.
   j. In cardiac surgery, perioperative tranexamic acid reduced blood product transfusions and rates of major hemorrhage without a higher risk of death from thrombotic complications, but with an increased risk of seizures (0.7% vs. 0.1%; p<0.01).
      i. Of note, the tranexamic acid doses of 50–100 mg/kg used in this study are much higher than those used in trauma.
      ii. The increased risk of seizures may be unique to cardiac surgery because the risk of stroke and seizures has been described after cardiac surgery, independent of tranexamic acid use.
2. Aminocaproic acid
   a. A lysine analog that is 10-fold less potent than tranexamic acid
   b. Recommended dose is a 150-mg/kg bolus, followed by a 15-mg/kg/hour infusion.
   c. Compared with tranexamic acid, aminocaproic acid may cause more adverse drug reactions, including hypotension and bradycardia, with rapid administration and rhabdomyolysis.
   d. Lower quality of evidence exists for aminocaproic acid in the treatment of the acutely bleeding patient.

J. Recombinant Activated Factor VIIa (rFVIIa)
1. Activates hemostasis through the extrinsic pathway of the coagulation cascade by interacting with tissue factor to activate factor X to factor Xa and factor IX to factor IXa. Adequate concentrations of platelets and fibrinogen are needed to support activity.
2. Case series and case reports suggest that rFVIIa improves clinical outcomes.
3. In trauma, a randomized controlled trial (CONTROL trial) was terminated early because of the futility for the primary end point of mortality, though investigators did find a reduction in PRBC transfusion with rFVIIa (200 mcg/kg followed by 100 mcg/kg at 1 hour and 3 hours) in patients with blunt trauma.
4. There is no consensus on rFVIIa use for acute bleeding. Institutional protocols vary with respect to appropriate indication, timing, dosing, and readministration of rFVIIa.
5. Database reviews document an increased incidence of venous and arterial thromboembolic events with off-label rFVIIa use for non-hemophilia indications.
6. In trauma, rFVIIa should only be considered if major bleeding and traumatic coagulopathy persist despite all other attempts to control bleeding and optimize the physiologic environment, including correction in acidosis, hypothermia, and hypocalcemia.
7. Although rFVIIa may reduce transfusion requirements, its lack of consistent mortality benefit limits its widespread adoption in trauma care.

K. Prothrombin Complex Concentrates (PCCs)
1. A combination of concentrated clotting factors II, VII, IX, and X and proteins C and S
   a. Four different forms of PCC are available in the United States. Factor content of the PCCs varies, particularly for factor VII (Table 5).
   b. FEIBA (factor eight inhibitor bypassing activity) is the only PCC composed of activated clotting factors, making it an activated prothrombin complex concentrate (aPCC). Although theoretically more efficacious, this may also lead to increased thrombotic events.

2. Kcentra, a nonactivated 4F-PCC, has U.S. Food and Drug Administration (FDA)-approved labeling for use in the reversal of warfarin-related acute bleeding disorders (further discussed under Reversal of Oral Anticoagulant Agents) in life-threatening hemorrhage or for urgent surgery or invasive procedures.
   a. Not indicated for the treatment of hemophilia-related bleeding because other PCC products are approved.
   b. The package insert warns of an increased thromboembolic risk with Kcentra administration. Kcentra is contraindicated in patients with known heparin-induced thrombocytopenia because the product contains heparin.
   c. Few data support the off-label use of PCCs as hemostatic agents in patients with bleeding not previously receiving anticoagulation; however, interest in this use and evidence are growing.
      i. The RETIC trial, which used PCC and concentrated fibrinogen compared with plasma in trauma patients with bleeding, was terminated early for safety concerns because of the high need of rescue therapy and massive transfusion in the plasma group.
      ii. In a double-blind, randomized, placebo-controlled superiority trial conducted in 12 French designated level I trauma centers, a total of 324 patients at risk of massive transfusion were included (PROCOAG randomized clinical trial). These patients received either intravenous 4F-PCC or a saline solution as treatment. The study's primary outcome was 24-hour all blood product consumption, and the secondary outcome was the occurrence of arterial or venous thromboembolic events. The results showed that there was no statistically or clinically significant difference in total 24-hour blood product consumption between the two groups. The 4F-PCC group consumed a median of 12 units of blood products, and the placebo group consumed a median of 11 units, with an absolute difference of 0.2 units (95% CI, -2.99 to 3.33; p=0.72). The study also showed that thromboembolic events were more common in the 4F-PCC group, with 35% of patients in this group experiencing at least one such event, compared with 24% in the placebo group. The absolute difference was 11% (95% CI, 1%–21%), with a relative risk of 1.48 (95% CI, 1.04–2.10; p=0.03). These findings do not support the routine use of 4F-PCC in such patients.
      iii. Although use of coagulation factor concentrates (CFCs) for hemostatic resuscitation is less common in the United States, the 2019 European trauma guidelines recommend CFCs as an alternative to plasma.

Table 5. Factor Content of PCCs Available in the United States

	Factor II (IU)	**Factor VII (IU)**	**Factor IX (IU)[a]**	**Factor X (IU)**	**Additives[b]**	**Vial Dose (estimated factor IX IU)**
3-factor PCC[c]						
Bebulin VH	100	< 5	100	100	Trace heparin	200–1200
Profilnine	150	35	100	100	N/A	500, 1000, 1500
4F-PCC[d]						
Kcentra	106.9	55.1	100	141.4	Protein C, S, Z, antithrombin III, heparin	500, 1000
aPCC[e]						
FEIBA	91.7–125	68-135	100	80–93.3	Protein C	500, 1000, 2500

[a] Expressed as international units (IU) per 100 IU of factor IX; the individual factor contents vary depending on vial size and can be determined by multiplying the individual factor content of interest by vial dose and dividing by 100 IU of factor IX equivalent.

[b] Anticoagulant factors in some PCC products are added to attenuate excessive thrombogenicity.

[c] Considered a 3-factor PCC because of limited amounts of factor VII.

[d] Considered a 4-factor PCC (4F-PCC) because of a significant concentration of factor VII.

[e] FEIBA is an aPCC that contains mainly nonactivated factors II, IX, and X; factor VII is mainly in the activated form.

FEIBA = factor eight inhibitor bypassing activity; N/A = not applicable.

Information from: Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. Neurocrit Care 2016;24:6-46; FEIBA NF [prescribing information]. Baxter Healthcare, 2011.

Patient Case

Questions 3 and 4 pertain to the following case.
D.R. is a 37-year-old man with an unknown medical history who presents after a helmeted motorcycle collision into a deer. On primary survey, his endotracheal tube is secured, respiratory rate is 37 breaths/minute, SBP is 72 mm Hg, heart rate is 141 beats/minute, and Glasgow Coma Scale score is 5T. His FAST examination is positive. An MTP is initiated, and the patient is taken to the operating room for an emergency exploratory laparotomy.

3. Which is the best initial resuscitation strategy to manage his hypotension?
   - A. Initiate a sodium chloride (0.9%) 3000-mL bolus to maintain a MAP over 65 mm Hg.
   - B. Obtain an Hgb concentration to guide erythrocyte transfusions, with goal Hgb 7–9 g/dL.
   - C. Initiate a norepinephrine infusion to maintain an SBP goal of 80–90 mm Hg.
   - D. Initiate PBRCs, plasma, and platelets in a 1:1:1 ratio on the basis of clinical examination.

4. In the operating room, the patient is found to have grade 5 hepatic laceration and grade IV spleen injury status after perihepatic packing and splenectomy. His abdomen is left open with a wound vacuum-assisted closure, and he is taken to the ICU. On arrival to the ICU (5 hours after injury), an arterial blood gas reveals a pH 7.18, partial pressure of carbon dioxide 22 mm Hg, lactate 12.7 g/dL, and $Pa\text{O}_2$ of 86% on 40% $F\text{IO}_2$ with assist control ventilation. He has received 14 units of erythrocytes, 12 units of plasma, and 12 units of platelets. His laboratory values include aPTT 37 seconds, INR 1.3, Hgb 7.5 g/dL, and Plt 154,000/mm^3. His temperature is 99°F (37.2°C) and ionized calcium is 0.7 mmol/L. Which is the best pharmacologic treatment strategy to manage his ongoing hemorrhagic shock in a goal-directed fashion?
   - A. Infuse 150 mEq of sodium bicarbonate in 1 L of sterile water at 200 mL/hour.
   - B. Give 1 g of calcium chloride once infused over 1 hour.
   - C. Give rFVIIa 90 mcg/kg once intravenous push.
   - D. Give a tranexamic acid 1000-mg bolus and 1000 mg infused over 8 hours.

L. Reversal of Oral Anticoagulant Agents (Table 6)
   1. Patient selection
      a. Assessment of bleed severity in patients treated with oral anticoagulants is critical to guide decisions related to reversal.
      b. The American College of Cardiology (ACC) 2020 expert consensus decision pathway suggests consideration for anticoagulation reversal in a major bleed, generally defined as bleeding into a critical site, hemodynamic instability, or clinically overt bleeding.
         i. Critical bleed site:
            (a) Bleeding in a critical site can compromise the organ function, may cause severe disability, and can potentially require surgical intervention.
            (b) These sites include: intracranial, other central nervous system (spinal, ocular), thoracic (e.g., pericardial tamponade, hemothorax), intra-abdominal, retroperitoneal, airway bleeding associated with respiratory distress, or extremity bleeding (e.g., intraarticular, intramuscular) causing compartment syndrome
            (c) Intraluminal GI bleeding is not considered a critical site; however, GI bleeding may be considered a major bleed on the basis of hemodynamic or overt bleeding criteria.

- ii. Hemodynamic instability is defined as a mean arterial pressure (MAP) less than 65 mm Hg, SBP less than 90 mm Hg, SBP decrease by at least 40 mm Hg, or orthostatic blood pressure changes (SBP decrease of at least 20 mm Hg, diastolic blood pressure [DBP] decrease of at least 10 mm Hg upon standing).
- iii. Overt bleeding, with a hemoglobin decrease of at least 2 g/dL within 24 hours, or requiring the administration of at least 2 units of PRBCs, is associated with increased mortality, particularly in patients with chronic cardiovascular disease.
- iv. Recommendations for managing a major bleed:
  - (a) Discontinue the anticoagulant, provide manual compression if the obvious bleed site is known or visualized, provide supportive care, assess and manage comorbidities that could contribute to bleeding (e.g., thrombocytopenia, uremia, liver disease, antiplatelets), and consider surgical or procedural management of the bleeding site.
  - (b) Specific anticoagulation reversal is indicated for bleeds at a critical site or those causing hemodynamic instability. For overt bleeding, initial bleeding control procedures are recommended, and reversal is indicated if the earlier measures fail to control the bleed.
  - (c) Supportive care: Transfusions, use of fibrinogen concentrates or cryoprecipitate, and correction of underlying coagulopathies (eg, liver dysfunction, platelet dysfunction)

2. Warfarin
   - a. Warfarin has a long physiologic half-life; thus, the reversal decision is usually based on the presence of an elevated INR in a life-threatening hemorrhage or the need for urgent surgery or an invasive procedure within 24 hours.
   - b. Phytonadione (vitamin K) administration is the definitive reversal of warfarin, promoting hepatic production of vitamin K–dependent clotting factors depleted by warfarin.
     - i. In life-threatening hemorrhage, injectable phytonadione at a dose of 5–10 mg given intravenously is preferred.
     - ii. Previous reports of anaphylaxis are related to solubilizing agents no longer included in the formulation.
     - iii. Phytonadione has a delayed onset (6–12 hours); therefore, clotting factors are given concurrently to expedite reversal.
   - c. Clotting factors can be given as either plasma or PCC.
     - i. Plasma has traditionally been used, but it requires large volumes, leads to incomplete INR correction, requires compatibility testing, and requires an extended time to achieve hemostasis.
     - ii. Evidence to support 4F-PCC over plasma:
       - (a) Compared with plasma in life-threatening hemorrhage, 4F-PCC is superior for laboratory reversal, is noninferior for clinical hemostasis, significantly reduces all-cause mortality, and has a similar rate of thromboembolic events.
       - (b) In an urgent surgical or invasive procedure, 4F-PCC is superior for rapid INR reversal and achievement of hemostasis.
       - (c) An integrated analysis of both life-threatening hemorrhage and urgent surgical trials suggests similar rates of thromboembolic events (4F-PCC 7.3% vs. fresh frozen plasma 7.1%), with fluid overload more common in the plasma group (4F-PCC 12.7% vs. fresh frozen plasma 4.7%). Although nonactivated 4F-PCC has a black box warning for an increased risk of arterial and venous thromboembolic events, this risk appears to be similar to that of plasma.
       - (d) Although 4F-PCC is associated with a high direct acquisition cost, pharmacoeconomic analyses are investigating similar strategies for warfarin reversal to fully understand the cost implications.
     - iii. rFVIIa is no longer recommended for warfarin reversal because of incomplete correction of factor concentrations inhibited by warfarin.

iv. Recommendations in a life-threatening hemorrhage:
   (a) Phytonadione 10 mg intravenously and a 4F-PCC (dose is determined by patient weight and pretreatment INR; see Table 7) are preferred for most patients.
   (b) Fixed dose 4F-PCC (e.g., 1000–1500 units) has been evaluated for warfarin reversal showing correction of the INR, but the lower dose may fail to correct the INR to goal, necessitating additional treatment. The 2020 ACC guidelines consider fixed low dose (1000 units for non-intracranial major bleed and 1500 units for intracerebral hemorrhage) as an alternative to the package insert dosing, but this is off-label and has lower-quality supporting evidence.
   (c) In patients with a contraindication to 4F-PCC (e.g., a history of heparin-induced thrombocytopenia), fresh frozen plasma 10–15 mL/kg or non-heparin containing PCC may replace 4F-PCC for reversal.
   (d) Although the goal INR is controversial, the 2016 Neurocritical Care Society guidelines recommend trending an INR in patients with intracranial hemorrhage with repeat reversal strategies until the INR is less than 1.4. Randomized controlled trials of 4F-PCC included only patients with an INR of 2 or greater.

3. Direct oral anticoagulants (DOACs) – Dabigatran/apixaban/rivaroxaban/edoxaban:
   a. Coagulation assays that have direct, linear relationships to the DOAC anticoagulation activity are not available for clinical use (Table 6).
   b. Therefore, the initial approach to reversal should be guided by clinical bleeding and the knowledge of preexisting DOAC use rather than coagulation assays.
   c. Given the relatively short DOAC half-life in patients with normal end-organ function, establishing the time from the last dose is critical in determining whether the drug is contributing to bleeding. In general, if it has been more than 3–5 half-lives since the last dose, reversal is probably not indicated (Table 6).

Table 6. Summary of Oral Anticoagulants

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Action	Vitamin K antagonist	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Peak action	4–5 days	~2 hr	~2 hr	~2 hr	1–2 hr
Half-life (hr)					
CrCl: > 80	> 48 hr	12–14	5–9	8–15	8.5
CrCl: 50–79		17	9	15	9
CrCl: 30–49		19	9	18	9
CrCl < 30		28	10	17	9.5
Clinical coagulation monitoring	Protime/INR: Quantitative	aPTT and TT: Qualitative ECT and dilute TT: Quantitative	Protime Rivaroxaban, edoxaban: Qualitative, if validated Apixaban: Insensitive Chromogenic anti-Xa: Quantitative Heparin or low-molecular-weight heparin assay: Qualitative		

anti-Xa = anti-factor Xa; CrCl = creatinine clearance reported as mL/min/1.73 m^2; ECT = ecarin clotting time; TT = thrombin time.
Information from: Dager WE. Developing a management plan for oral anticoagulation reversal. Am J Health Syst Pharm 2013;70:S21-31.

   d. Activated charcoal may be considered if the last dose was administered less than 2 hours previously. Given significant enterohepatic recirculation, charcoal can be given up to 6 hours after the last apixaban dose.

e. Dabigatran reversal: Idarucizumab is FDA approved for dabigatran reversal.
    i. Idarucizumab is a monoclonal antibody that binds both bound and unbound dabigatran. It has a binding affinity to dabigatran that is greater than 350 times that of dabigatran for thrombin.
    ii. In the RE-VERSE AD trial, in the full analysis of 503 patients with life-threatening hemorrhage or need for urgent procedure, all who received idarucizumab 5 g intravenously had maximum dilute TT reversal by 4 hours after idarucizumab administration. Given that dabigatran has a volume of distribution of greater than 50 L, about 23% of patients developed redistribution of unbound dabigatran and associated coagulopathy at 12–24 hours. The efficacy of repeat doses in this setting has not been established. The package insert recommends that if there is clinically relevant bleeding (or need for a second emergency surgery/urgent procedure) in combination with elevated coagulation parameters (e.g., aPTT, ecarin clotting time), an additional 5-g dose of idarucizumab may be considered. Therefore, an aPTT should be obtained to rule out the presence of dabigatran before a repeat dose is given.
    iii. The thrombotic event rate at 90 days was 6.8%. All thrombotic events that occurred within 72 hours were in patients for whom anticoagulation was not reinitiated (also because of half-life of 45 minutes).
    iv. Given the availability of idarucizumab, adjunctive reversal options such as dialysis should only be considered if there are concurrent indications on the basis of renal function or if idarucizumab is ineffective.

f. Factor Xa inhibitors: Andexanet alfa is FDA approved for rivaroxaban and apixaban reversal in life-threatening hemorrhage.
    i. Andexanet alfa is a modified factor Xa decoy protein such that it directly binds to the factor Xa inhibitors in a 1:1 ratio to inactivate their anticoagulant response.
        (a) Andexanet alfa structural modifications render it incapable of having prothrombotic or antithrombotic effects.
        (b) Mutation of the active serine site ensures that andexanet lacks the catalytic activity needed to convert prothrombin to thrombin.
        (c) Deletion of the GLA fragment makes andexanet unable to bind to phospholipids and interact with factor V and calcium to form a prothrombinase complex.
    ii. Andexanet alfa reverses the effects of both direct (DOAC) and indirect (low-molecular-weight heparin) factor Xa inhibitors.
    iii. The ANNEXA-4 trial evaluated the effects of andexanet alfa in patients with acute major bleeding and recent ingestion of factor Xa inhibitors, predominantly apixaban and rivaroxaban.
        (a) After an initial bolus of andexanet, there was a 90%–92% reduction in the anti-factor Xa (anti-Xa) activity from baseline. This was sustained through the 2-hour infusion of the study drug, allowing for a hemostatic plug to form.
        (b) Of note, only 72% of patients met the predefined threshold for anticoagulation activity (baseline anti-Xa concentrations of 75 ng/mL or greater for DOACs or 0.25 IU/mL or greater for enoxaparin) to be included in this efficacy analysis.
        (c) An important limitation of this study was the exclusion of patients expected to require surgery within 12 hours, a population commonly encountered when treating bleeding patients.
    iv. Andexanet alfa has a short half-life (1 hour); thus, redistribution and associated anticoagulant activity are also common after discontinuing andexanet.
        (a) In theory, this 2-hour time interval allows for a hemostatic plug to form and bleeding to stop.
        (b) In the ANNEXA-4 trial, anti-Xa activity rebounded. Two hours after discontinuing the infusion, anti-Xa activity decreased only 32%–42% relative to baseline.
        (c) However, at 12 hours, 82% of patients met the co-primary end point of good or excellent clinical hemostasis. This brings into question the clinical significance of the rebound effect. Further research is needed to determine the importance of this rebound effect in patients with ongoing bleeding, patients with critical site bleeds, or surgical populations.

v. Anticipated limitations when using andexanet in clinical practice:
    (a) The largest limitation of the ANNEXA-4 trial is the lack of a control group, with little ability to determine how andexanet affects patient-centered outcomes.
    (b) Given that only 72% of patients were eligible for the efficacy analysis, these results may have an exaggerated effect relative to that of the general population.
    (c) One of the greatest concerns is the relative short duration of laboratory reversal, given the short half-life of andexanet alfa and its reversible binding with anti-Xa inhibitors.
    (d) Implications are unclear for patients who continue to have clinical evidence of bleeding beyond the andexanet infusion and the need to repeat doses or extend infusions.
    (e) Notable exclusion criteria from this trial include requirement of surgery as well as severe brain injury (average GCS score was 14). Implications of short-term reversal may be even greater for these high-acuity patient populations.

vi. Safety of andexanet alfa:
    (a) 10% of the population had a thrombotic event, with most occurring before the initiation of therapeutic anticoagulation.
    (b) Andexanet alfa does bind to tissue factor pathway inhibitor, an endogenous factor Xa inhibitor.
    (c) This rate is generally higher than what has been shown for other reversal agents in bleeding patients, including PCCs for warfarin reversal (7%–8%) and idarucizumab for dabigatran reversal (6.35%–7.4%).
    (d) It is important to recognize differences in population risks that confound cross-study comparisons, given that the updated ANNEXA-4 analysis included at least double the population with intracranial hemorrhage compared with other reversal studies. In this setting, reintroduction of anticoagulation may be delayed.

vii. The ANNEXA-I trial was a multicenter, multinational, randomized, open-label study designed to compare the efficacy and safety of andexanet alfa with usual care in patients experiencing acute intracerebral hemorrhage while receiving factor Xa inhibitors. The primary objective was to evaluate hemostatic efficacy 12 hours after randomization using end points such as a 35% or less change in hematoma volume, an increase in the 12-hour NIHSS (NIH Stroke Scale) score of less than 7 points, and the avoidance of rescue therapies between 3 and 12 hours after randomization. The trial was designed to achieve 90% power to detect a 10% absolute difference in hemostatic efficacy, targeting 900 patients. The primary analysis included 452 patients, with 224 in the andexanet alfa group and 228 in the usual care group. Of note, 85.5% of the usual care group received 4F-PCC. At baseline, intracerebral hemorrhage was present in 88.4% of patients in the andexanet alfa group and 93.9% in the usual care group. Subdural hematomas (SDHs) were reported in 5.8% of the andexanet alfa group compared with 1.8% in the usual care group. The NNT for efficacy was 8, indicating that 8 patients required treatment with andexanet alfa for 1 patient to benefit over usual care. However, the NNH was 21, highlighting increased risks, including ischemic stroke rates of 6.5% in the andexanet alfa group versus 1.5% in the usual care group and myocardial infarction reported at 4.2% versus 1.5%, respectively. Critiques of the ANNEXA-I trial pointed to notable limitations affecting its clinical applicability. One significant concern was the use of composite end points. Around 15% of the usual care group did not receive active treatment, and there was limited understanding of 4F-PCC agents and appropriate dosing during the trial. When analyzing the full patient population, efficacy decreased from 67% to 63.9%, raising questions about the overall benefit. Despite the trial's focus on intracerebral hemorrhage, higher rates of SDH were observed in the andexanet alfa group (5.8% vs 1.8% in the usual care group). In addition, the absence of long-term follow-up beyond 30 days restricted insights into the sustained benefits and outcomes of the treatment.

- viii. Andexanet alfa dosing is complex (Table 7) and individualized according to the underlying anticoagulant and time from last dose. For example, rivaroxaban achieves higher serum concentrations, so andexanet doses are higher for rivaroxaban with recent administration than for apixaban.
- ix. Although andexanet alfa may work for all direct and indirect anti-Xa inhibitors, it is only FDA approved for apixaban and rivaroxaban reversal in life-threatening or uncontrolled bleeding.
  - (a) Use for other anticoagulant-related bleeding is off-label, with overall lower supporting evidence.
  - (b) If used for edoxaban or enoxaparin, the dose under investigation is high dose.

g. The antidotes for DOAC reversal were FDA reviewed under the Fast Track designation.

- i. The FDA called for the inclusion of an andexanet alfa arm compared with a usual care arm for anti-Xa reversal in patients experiencing intracranial hemorrhage. The ANNEXA-I study was designed to compare the effectiveness of andexanet alfa with usual care in treating intracranial hemorrhage. This trial was necessary because prior studies, such as ANNEXA-4, did not randomize patients to a placebo group, and efficacy and safety data were based on single-arm trials. The results of the trial indicate that ANNEXA-I met its prespecified criteria for hemostatic efficacy when compared with standard care. These promising results prompted the early termination of the study after a planned interim analysis. The data suggested an NNT of 8, showing significant efficacy. However, this benefit was counterbalanced by a higher incidence of adverse events, including thrombotic complications such as ischemic stroke and myocardial infarction, with an NNH of 21. The increased risk of thrombotic events highlights the need for careful consideration of the treatment's safety profile.
- ii. Therefore, it remains unknown whether the novel antidotes will affect morbidity or mortality associated with anticoagulants in life-threatening hemorrhage.

h. PCCs for DOAC reversal

- i. PCCs and aPCCs have traditionally been used off-label as a nonspecific reversal agent for DOAC reversal before the development of novel antidotes.
- ii. Supporting data are primarily based on laboratory reversal of factor Xa inhibitors from in vitro animal models, ex vivo human samples, and healthy volunteer subjects. These trials have important limitations and inconsistent results.
- iii. More recently, PCC was an effective reversal for anti-Xa inhibitors in bleeding patients, as evaluated by hemostatic response at defined time intervals, but these trials are limited by single-arm observational study design and lack of analysis of laboratory reversal.
- iv. PCC has not consistently been shown to reverse laboratory values associated with dabigatran.
- v. Several guidelines recommended 4F-PCC or aPCC administration at 25–50 units/kg for anti-Xa reversal before the availability of andexanet alfa. Guidelines may continue to evolve as more robust data comparing andexanet alfa with usual care become available. Clinicians should carefully consider the non-sustained duration of reversal of andexanet alfa and the lack of data in emergency surgical procedures.
- vi. Use of PCCs and aPCCs carries a risk of thromboembolic events, particularly at higher doses, necessitating a careful risk-benefit assessment.
- vii. Further studies comparing andexanet alfa with PCC-based regimens in real-world clinical scenarios

Table 7. Anticoagulant Reversal Agent Dosing in Life-Threatening Hemorrhage

Which Anticoagulant		**Reversal Agent**	**Dose**
Warfarin with elevated INR		4F-PCC	INR 2 to < 4: 25 units/kg (max 2500 units) INR 4–6: 35 units/kg (max 3500 units) INR > 6: 50 units/kg (max 5000 units)
Dabigatran within 3–5 expected half-lives		Idarucizumab	5 g IV push once Limited data to repeat 5 g
Factor Xa inhibitor within 3–5 expected half-lives			
Agent	**Last Dose**	Andexanet alfa	Low dose: 400-mg bolus at a target rate of 30 mg/min, 4 mg/min for 120 min High dose: 800-mg bolus at a target rate of 30 mg/min and 8 mg/min for 120 min *If time from last dose not known, use appropriate dose if consumed within 8 hr*
Rivaroxaban	≤ 10 mg: Low dose > 10 mg within 8 hr: High dose > 10 mg after ≥ 8 hr: Low dose		
Apixaban	≤ 5 mg: Low dose > 5 mg within 8 hr: High dose > 5 mg after ≥ 8 hr: low dose		
Edoxaban Enoxaparin	High dose at any time *Off-label*		
Which Anticoagulant		**Reversal Agent**	**Dose**
Direct and indirect anti-Xa inhibitors		4F-PCC aPCC *Off-label*	25–50 units/kg

IV = intravenous(ly).

Information from: Sarode R, Milling TJ, Refaai MA, et al. Efficacy and safety of 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013;128:1234-43; Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20; and Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016;365:1131-41.

M. Reversal of Antiplatelet Agents (Table 8)
  1. Controversies remain regarding the impact of antiplatelet agents on traumatic bleeding.
  2. The PATCH trial was the first randomized controlled trial evaluating the impact of platelet transfusions for spontaneous intracranial hemorrhage in patients receiving antiplatelet therapy for at least 7 days prior.
     a. Odds of death were higher in the platelet transfusion group at 3 months than in placebo (adjusted OR 2.05; 95% CI, 1.18–3.56; p=0.0114), suggesting platelet transfusions are inferior to standard of care in non-operative patients.
     b. Study limitations include the lack of platelet function tests, inability to ensure medication adherence before the event, exclusion of surgical patients, and predominant use (greater than 90%) of aspirin as the antiplatelet agent.
     c. PATCH trial findings are specific to spontaneous intracranial hemorrhage in nonsurgical patients and may not directly apply to trauma or other settings. Platelet transfusion practices for traumatic hemorrhage require further randomized controlled trials.
  3. The 2019 European guidelines for managing traumatic bleeding recommend platelet transfusions in patients who have been treated with antiplatelet agents in the following scenarios:
     a. Continued bleeding with documented platelet dysfunction (grade 2C)
     b. Intracranial hemorrhage undergoing surgery (grade 2B)

4. Desmopressin enhances platelet adherence and aggregation.
    a. Although its clinical efficacy is controversial, desmopressin 0.3–0.4 mcg/kg intravenously may be considered to reverse platelet-inhibiting drugs or von Willebrand disease but may not be routinely used in trauma patients with bleeding. If administering desmopressin, the 2019 European trauma guidelines recommend administering an antifibrinolytic (e.g., tranexamic acid) in parallel.
    b. There is a low risk of serious adverse effects, including hypervolemia, hyponatremia, facial flushing, and rare thrombosis.

Table 8. Antiplatelet Reversal in Life-Threatening Hemorrhage

Generic Drug (trade name): Mechanism of Action	Coagulation Assay Effects	Usual Half-Life (hr)	Duration of Platelet Inhibition	Recommendations
Aspirin Inhibits platelet activation Irreversible inhibition of COX-1 and COX-2 enzymes	Optimal platelet function assay and thresholds controversial Light transmission platelet aggregation is gold standard of platelet function testing but is not routinely available TEG with platelet mapping, VerifyNow, platelet function analyzer, and bleeding time may be used	3	Lifetime of platelets 5–7 days	Use caution with antiplatelet reversal in patients with active or recent (within 3 mo) coronary artery disease Reversal strategies: **Platelets*** Neurosurgical hemorrhage: 1 apheresis unit (moderate quality of evidence) Neurosurgery is not indicated: Platelet transfusions controversial and not recommended by the Neurocritical Care Society (low quality of evidence) -and/or- **Desmopressin (DDAVP) 0.4 mcg/kg IV push once** (low quality of evidence) *Transfused platelets with ticagrelor may become inhibited because of reversible activity at the P2Y12 receptor
Dipyridamole ± aspirin (Aggrenox, Persantine) Inhibits platelet activation Increases endogenous adenosine		10–12	2–3 days (dipyridamole) Lifetime of platelets 5–7 days for aspirin	
Clopidogrel (Plavix) Inhibits platelet activation Active metabolite irreversibly blocks ADP		6	Lifetime of platelets 5–7 days	
Prasugrel (Effient) Inhibits platelet activation Active metabolite irreversibly blocks ADP		2–15	Lifetime of platelets 5–7 days	
Ticagrelor (Brilinta) Inhibits platelet activation Reversibly blocks ADP		7–9	3–5 days	

AA = arachidonic acid; ADP = adenosine diphosphate; COX = cyclooxygenase.

Information from: Levi M, Eerenberg E, Kamphuisen PW, et al. Bleeding risk and reversal strategies for old and new anticoagulants and antiplatelet agents. J Thromb Haemost 2011;9:1705-12; Mega J, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet 2015;386:281-91; Spahn D, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care 2019;23:98; Frontera JA, Lewin JJ, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage. Neurocrit Care 2016;24:6-46.

Patient Cases

5. A 54-year-old man with an unknown medical history presents after a rollover automobile accident. On primary survey, his respiratory rate is 34 breaths/minute, SBP is 79 mm Hg, and Glasgow Coma Scale score is 3. The FAST examination is positive, an MTP is initiated, and the patient is taken to the operating room for an emergency exploratory laparotomy. In the operating room, he is found to have grade 5 splenic injury, so the spleen is removed. Four hours after admission, he has received 14 units of PRBCs, 12 units of fresh frozen plasma, and 10 units of platelets. His laboratory values include aPTT 66 seconds, INR 1.7, fibrinogen 176 mg/dL, Plt 160,000/mm^3, and ionized calcium 1.1 mmol/L. The TEG is normal except for an LY30 of 0% (normal 0.8%–8%). The patient's wife arrives at the hospital and clarifies that he was out for a Sunday afternoon ride. She also shares that the patient has a history of atrial fibrillation and takes dabigatran (last dose this morning). Which is the best pharmacologic treatment of his ongoing hemorrhagic shock?
   - A. Administer 4F-PCC 50 units/kg.
   - B. Administer a tranexamic acid 1-g bolus with 1-g infusion over 8 hours.
   - C. Administer an idarucizumab 5-g intravenous push.
   - D. Administer an idarucizumab 5-g intravenous push and a tranexamic acid 1-g bolus, followed by 1 g infused over 8 hours.

6. B.P is a 76-year-old man (120 kg) with atrial fibrillation on warfarin admitted to the ED with weakness and hematemesis. Pertinent vital signs on admission are as follows: blood pressure 79/52 mm Hg, heart rate 136 beats/minute with a rhythm of sinus tachycardia, and respiratory rate 26 breaths/minute. Frank red blood is noted on nasogastric lavage. On physical examination, the patient is confused, with clammy extremities. Pertinent laboratory values are as follows: Hgb 6.3 g/dL, INR 9.2, and Plt 300,000/mm^3. In addition to intravenous phytonadione, which therapy is most appropriate for managing warfarin reversal in this patient?
   - A. 4F-PCC 1000 units.
   - B. 4F-PCC 5000 units.
   - C. rFVIIa 1-mg intravenous push.
   - D. 4F-PCC 6000 units.

II. OBSTRUCTIVE SHOCK

A. Etiology and Epidemiology
   1. Obstructive shock occurs because of extracardiac obstruction to flow in the cardiovascular system.
   2. The source of extracardiac obstruction may be either impaired diastolic filling (e.g., cardiac tamponade, tension pneumothorax, or constrictive pericarditis) or impaired systolic contraction (e.g., massive PE, acute or chronic PH or aortic dissection).
   3. Obstructive shock is relatively rare, and only about 2% of patients requiring vasoactive medications have this type of shock.

B. Pathophysiology
   1. The pathophysiologic hemodynamic hallmark of obstructive shock is decreased CO.
   2. The specific pathophysiologic derangements depend on the underlying cause of the extracardiac obstruction but are generalized as follows:

a. In impaired diastolic filling, RV preload is significantly decreased because of the inhibition of venous return.
    i. In cardiac tamponade, an accumulation of fluid in the pericardium leads to an increase in pericardial pressure.
    ii. This increases and equalizes diastolic pressures between the left and right heart (equalization of central venous pressure [CVP], pulmonary artery diastolic pressure, and pulmonary capillary wedge pressure [PCWP] and impaired ventricular filling). CVP and PCWP elevations should not be mistaken as representing an increase in ventricular volume (preload).
b. In impaired systolic function, ventricular afterload is acutely increased, leading to ventricular failure.
    i. This typically occurs in an acute RV afterload (pulmonary vascular resistance) increase caused by a massive PE or in acute PH.
    ii. An acute increase in LV afterload does not typically lead to shock.
    iii. An acute rise in RV afterload leads to reduced RV CO and a subsequent decrease in LV CO. Subsequently, systemic hypotension develops, leading to reduced RV tissue perfusion (decreased right coronary artery perfusion), RV free wall ischemia, reduced RV free wall contractility, and further impairment of RV CO (a vicious cycle).
    iv. In addition, acute RV pressure overload leads to a shift of the intraventricular septum toward the LV, impairing LV diastolic filling (because of intraventricular dependence) and further decreasing in LV CO.

C. Resuscitation and Treatment
1. Fluid administration and vasoactive medications may be used as a temporizing measure to increase tissue perfusion.
    a. Intravenous fluids (typically crystalloids) are usually recommended, but they may not improve CO.
        i. Cardiac tamponade: Patients with preexisting hypovolemia may respond to fluids, but in general, hemodynamics may not improve with fluid administration. Despite this finding, fluid administration is usually recommended in cardiac tamponade.
        ii. Massive PE: Initial fluid administration improves CO, but care should be taken because excessive fluid administration can lead to further RV dilation and impaired LV CO from worsened septal shifting and decreased LV filling (because of intraventricular dependence).
        iii. Acute or chronic PH: Optimization of fluids in patients with acute or chronic PH is challenging. Some patients, such as those with signs of intravascular volume depletion, may require fluids. Others may require diuretics to reduce RV dilation and improve LV filling, even with vasoactive medication administration.
    b. Vasopressors should be initiated to increase MAP and maintain an adequate perfusion pressure.
        i. This is particularly important in a massive PE because adequate right coronary artery perfusion is of greatest importance to prevent/reduce RV free wall ischemia.
        ii. Caution must be used because catecholamine vasopressors may increase pulmonary vascular resistance, which may worsen RV dysfunction.
    c. Inotropes may increase RV CO in a massive PE or acute or chronic PH but are likely ineffective in tamponade.
    d. Inhaled nitric oxide or aerosolized prostacyclin therapy may decrease RV afterload in acute or chronic PH, but neither therapy is likely effective for massive PE or cardiac tamponade.
2. Definitive treatment of the extracardiac obstruction is paramount.
    a. Impaired diastolic filling
        i. Cardiac tamponade: Pericardiocentesis or surgical evacuation and potential drain placement
        ii. Tension pneumothorax: Needle decompression and potential chest tube thoracostomy

b. Impaired systolic function (massive PE): Embolism dissolution (thrombolytic therapy) or removal (surgical or catheter thrombectomy)
   i. Thrombolytic agents (Table 9) bind to the plasminogen/plasmin complex, which may be either circulating or bound to the clot surface.
   ii. This binding hydrolyzes a peptide bond to form free plasmin. Circulating plasmin is quickly neutralized by α-antiplasmin, but fibrin-bound plasmin subsequently hydrolyzes bonds within the clot matrix, leading to clot lysis.
   iii. As such, thrombolytic agents can lead to rapid PE dissolution and a subsequent decrease in RV afterload (pulmonary vascular resistance), but they may also cause bleeding.

Table 9. Thrombolytic Agents for Acute PE

Drug	Dose		Pearl
	Initial	Infusion	
Alteplase[a]	Total dose: 100 mg infused over 2 hr		Fibrin selective half-life: 5 min Dose in cardiac arrest may be 50 mg
Reteplase[b]	Two doses of 10 units IV push over 2 min, given 30 min apart		Fibrin selective half-life: 13–16 min
Tenecteplase[b]	< 60 kg: 30-mg push over 5–10 s 61–70 kg: 35-mg push 71–80 kg: 40-mg push 81–90 kg: 45-mg push > 91 kg: 50-mg push	N/A	Fibrin selective (14-fold compared with alteplase) half-life: 90–130 min; only need bolus dose Less expensive than alteplase
Streptokinase[b]	250,000 units over 30 min	100,000 units/hr over 24 hr	Nonselective Antigenic
Urokinase[a]	4400 units/kg over 10 min	4400 units/kg/hr over 12 hr	Nonselective

[a] Indicates FDA approved for the treatment of PE.

[b] Indicates drug is not FDA approved for the treatment of PE.

PE = pulmonary embolism.

Information modified from: Daley MJ, Lat I. Clinical controversies in thrombolytic therapy for the management of acute pulmonary embolism. Pharmacotherapy 2012;32:158-72.

   iv. In a 2004 meta-analysis, thrombolytic agents were not shown to decrease mortality when evaluated among all patients with a PE compared with heparin alone (6.7% vs. 9.6%; OR 0.67 [95% CI, 0.40–1.12]), but they may improve outcomes in patients with an increased risk of death. As such, early PE-related mortality risk stratification is necessary to guide thrombolytic therapy administration.
      (a) High-risk or massive PE. Defined by the 2011 American Heart Association (AHA) guidelines not by clot burden, but by acute PE causing hemodynamic changes: Hypotension (SBP less than 90 mm Hg for at least 15 minutes or requiring vasoactive support not from another cause), pulselessness, or bradycardia (heart rate less than 40 beats/minute with signs of shock). The 2019 European Society of Cardiology (ESC) and European Respiratory Society (ERS) guidelines for acute PE define hemodynamic instability as including one of the following presentations:
         (1) Cardiac arrest,
         (2) Obstructive shock (SBP less than 90 mm Hg or vasopressors required to achieve SBP of 90 mm Hg or greater despite adequate filling status AND end-organ hypoperfusion), or

      (3) Persistent hypotension (SBP less than 90 mm Hg or SBP decrease of 40 mm Hg or greater for more than 15 minutes, not caused by new-onset arrhythmia, hypovolemia, or sepsis)
    (b) Intermediate-risk or submassive PE.
      (1) AHA 2011 classification: Acute PE without systemic hypotension but with either (1) RV dysfunction (RV dilation or systolic dysfunction on echocardiogram, RV dilation on chest CT, brain natriuretic peptide greater than 90 pg/mL, N-terminal pro-brain natriuretic peptide greater than 500 pg/mL, or electrocardiographic changes [new complete or incomplete right bundle-branch block, anteroseptal ST-segment elevation or depression, or anteroseptal T-wave inversion]) or (2) myocardial necrosis (troponin I greater than 0.4 ng/mL or troponin T greater than 0.1 ng/mL) (2) ESC/ERS 2019 classification: Simplified Pulmonary Embolism Severity Index score of 1 or greater (i.e., age older than 80; cancer, chronic respiratory disease, or cardiac disease; heart rate 110 beats/minute or greater; SBP less than 100 mm Hg; or Sa_{O_2} less than 90%), regardless of whether there is RV strain
    (c) Intermediate-risk PE may further be classified by the presence of both RV dysfunction and myocardial necrosis, termed *intermediate-high risk*. If only RV dysfunction or myocardial necrosis is present, it is classified as *intermediate-low risk*.
    (d) Low-risk PE: Acute PE not meeting the definition of massive or submassive PE
  v. Thrombolytics in cardiac arrest:
    (a) The 2020 AHA International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Circulation 2020;142:S92-S139) remains unchanged from the 2015 AHA guidelines, stating there is no consensus on the ideal thrombolytic dose in PE-associated cardiac arrest. Contemporary examples of dosing regimens include either an alteplase bolus of 50 mg (repeated if needed to complete a 100-mg intravenous total dose) or weight-based tenecteplase if PE is confirmed as the contributing cause of the arrest.
    (b) The 2020 AHA guidelines have a weak recommendation to administer fibrinolytic drugs for cardiac arrest when PE is the suspected cause of cardiac arrest (very low-certainty evidence). When PE is the confirmed cause of cardiac arrest, fibrinolytic drugs or surgical embolectomy or percutaneous mechanical thrombectomy may be used (very low-certainty evidence). The task force considered increased bleeding risk from fibrinolytics administered to patients who may not have PE. In the TROICA study, the largest study of thrombolysis during cardiac arrest, thrombolysis was associated with increased bleeding risk but no difference in major bleeding complications. The task force concluded that patients are far more likely to die from cardiac arrest than from treatment.
    (c) These recommendations are based on possible improved outcomes with thrombolytics in peri-arrest settings, but prospective evaluations are conflicting.
  vi. Thrombolytics in massive PE:
    (a) The 2021 update to the CHEST guidelines and the 2019 ESC/ERS guidelines recommend systemic thrombolytics for patients with a massive/high-risk PE and an acceptable risk of bleeding complications.
    (b) These recommendations are supported by a meta-analysis, which found that in patients with a massive PE, thrombolytics were associated with a lower rate of recurrent PE or death than heparin alone (9.4% vs. 19.0%; OR 0.45 [95% CI, 0.22–0.92]).

- (c) A 2012 analysis of a National Inpatient Sample containing over 70,000 patients with an unstable PE (defined as the presence of shock or a requirement for mechanical ventilation) suggested reduced mortality attributable to PE with the use of systemic thrombolytics (8.4% vs. 42%; p<0.0001).
- (d) Systemic thrombolytics for a massive PE are likely underused because about 70% of patients in this database were not treated.

vii. Use of thrombolytics in submassive PE is controversial and should be based on the risk-benefit profile:

- (a) In a study of patients with a submassive PE, adding alteplase 100 mg infused over 2 hours to heparin compared with heparin plus placebo (heparin alone) was associated with a lower rate of death or clinical deterioration requiring an escalation in treatment (11.0% vs. 24.6%, p=0.006). This result was driven by more patients in the heparin-alone arm who received secondary thrombolytics (23.2% vs. 7.6%, p=0.001), which may have been influenced by the investigators' ability to break the blinding of treatment allocation in the study. Bleeding did not differ between study arms.
- (b) The PEITHO study evaluated patients with a submassive PE (fulfilling both RV dysfunction and myocardial necrosis criteria) randomized to weight-based tenecteplase plus heparin or placebo plus heparin (heparin alone).
  - (1) Between randomization and day 7, patients allocated to tenecteplase less commonly died or had hemodynamic decompensation (2.6% vs. 5.6%, p=0.02; number needed to treat 33 patients [95% CI, 18–162 patients]) but more commonly had major extracranial bleeding (6.3% vs. 1.2%, p<0.001; number needed to harm 20 patients [95% CI, 13–35 patients]) and stroke (2.4% vs. 0.2%, p=0.003; number needed to harm 47 patients [95% CI, 26–107 patients]).
  - (2) The difference in stroke incidence was driven by a higher incidence of hemorrhagic stroke in the tenecteplase arm (2.0% vs. 0.2%, p=0.01; number needed to harm 57 patients [95% CI, 30–164 patients]).
  - (3) The overlapping 95% CIs for number needed to treat and number needed to harm for clinically important outcomes call into question the risk-benefit profile of tenecteplase for a submassive PE.
- (c) Around 70% of patients from the PEITHO trial had a long-term follow-up for at least 24 months (average 37.8 months).
  - (1) Overall and cause-specific mortality at 30 days or long term did not differ in those who received tenecteplase compared with placebo.
  - (2) Of the 290 patients who had echocardiograms with long-term follow-up, CTEPH was confirmed in 2.1% of those who received tenecteplase compared with 3.2% who did not (p=0.79).
  - (3) In addition, functional status, symptoms, RV dysfunction, and survival by day 30 did not differ between tenecteplase and placebo.
- (d) As a result of this trial, the 2021 CHEST guidelines and the 2019 ESC/ERS guidelines recommend against routine use of systemic thrombolytics in intermediate- or low-risk PE. However, in select patients with signs or risk of deterioration and a low bleeding risk, systemic thrombolytics may be considered.

viii. The risk-benefit of thrombolytics is best determined on a case-by-case basis by the bedside clinician (Table 10).

- (a) In the PEITHO trial, a subgroup analysis showed that age older than 75 may be associated with a risk of major extracranial bleed (OR 20.38; 95% CI, 2.69–154.53; p=0.09).

  (b) Commonly used bleeding scores such as HAS-BLED moderately predict the risk of an intracranial hemorrhage after thrombolytic agents for PE but lack precision. HAS-BLED has not been validated specifically for predicting thrombolytic-associated bleeding in PE and should be used cautiously.

ix. In extreme circumstances (e.g., massive PE with impending cardiac arrest), even the presence of strong risk factors for bleeding may not preclude some clinicians from administering thrombolytics because of the potential for benefit from the therapy. In these settings, even the “contraindications” noted in the product labeling, other than active internal bleeding, may be considered “relative contraindications” by some clinicians for thrombolytic administration.

Table 10. Risk Factors for Bleeding After Thrombolytic Therapy

Alteplase package insert contraindications	
Active internal bleeding	Recent (within 3 mo) intracranial or intraspinal surgery or serious head trauma
Current cerebrovascular accident (intracranial hemorrhage or ischemic stroke)	Current severe uncontrolled hypertension[a]
Malignant intracranial neoplasm, arteriovenous malformation, or aneurysm	Known bleeding diathesis[b]
Alteplase package insert warnings	
Recent major surgery	Significant closed-head or facial trauma with radiographic evidence of bony fracture or brain injury within 3 mo
Cerebrovascular disease	Recent GI or genitourinary bleeding
Hemostatic defects (including those secondary to severe hepatic or renal disease)	Hypertension (SBP ≥ 175 mm Hg and/or DBP ≥ 110 mm Hg)
Acute pericarditis	Subacute bacterial endocarditis
Recent trauma	Significant hepatic dysfunction
Age > 75	Needle puncture at noncompressible site
Left heart thrombus	Pregnancy
Septic thrombophlebitis or occluded arteriovenous cannula at seriously infected site	Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
Recent receipt of oral anticoagulants	
Bleeding risk factors reported in published literature	
Recent internal bleeding	Suspected aortic dissection
Poorly controlled baseline hypertension[a]	Acute pancreatitis
Acute myocardial infarction	Cardiopulmonary resuscitation > 10 min
Stool occult blood positive	Bilirubin concentration > 3 mg/dL
Presence of an intra-aortic balloon pump	Dementia
African American race	Coagulopathy[b]

[a] Undefined for PE, but noted as > 185 mm Hg systolic or > 110 mm Hg diastolic for acute ischemic stroke.

[b] Undefined for PE, but noted as INR > 1.7 or Plt < 100,000/mm3 for acute ischemic stroke.

Adapted with permission from: Curtis GC, Lam SW, Reddy AJ, et al. Risk factors associated with bleeding after alteplase administration for pulmonary embolism: a case-control study. Pharmacotherapy 2014;34:818-25; and Daley MJ, Lat I. Clinical controversies in thrombolytic therapy for the management of acute pulmonary embolism. Pharmacotherapy 2012;32:158-72.

x. Catheter-directed thrombolysis (CDT) is an emerging treatment that enables the administration of lower-dose thrombolytic agents directly into the thrombus.
  (a) CDT has the advantage of concurrent mechanical disruption, including ultrasound-assisted fragmentation, aspiration, or embolectomy.
  (b) Applying CDT, several clinical trials have shown improved hemodynamics and strain on the RV with minimal risk of a major bleed (less than 1%).
  (c) However, prospective comparative studies evaluating long-term outcomes with CDT are currently lacking, and the site experiences and resources required limit widespread use.
  (d) The 2021 CHEST guidelines recommend systemic thrombolytic therapy over CDT for most patients; however, CDT may be considered in patients with acute PE associated with hypotension who also have high bleeding risk, failed systemic therapy, or shock likely to cause death before systemic thrombolysis can take effect.

xi. Reduced-dose thrombolytic therapy has been investigated as a strategy to minimize bleeding risk.
  (a) Several trials have evaluated “half-dose” alteplase compared with full dose, showing improved hemodynamic parameters and potentially less bleeding, but all trials had severe methodological limitations that limit generalizability.
  (b) A retrospective database of 3768 patients showed that patients who received half-dose alteplase were more likely to require treatment escalation (53.8% vs. 41.4%; $p<0.01$) driven by secondary thrombolysis without notable difference in bleeding complications.
  (c) Given the available data, experts do not recommend consideration for half-dose in PE management. For patients who need reperfusion treatment because of hemodynamic decompensation but who have absolute or relative contraindications to systemic fibrinolysis, CDT is recommended.
  (d) The PEITHO-3 trial (NCT04430569) aims to compare the efficacy and safety of reduced-dose alteplase with standard heparin in patients with intermediate-high risk PE. Results are expected to have a major impact on risk-adjusted acute PE treatment and guideline recommendations.

xii. Patients with a massive or submassive PE should be considered for surgical embolectomy or catheter thrombectomy if they (1) have an unacceptably high risk of bleeding if administered thrombolytics, (2) remain unstable despite thrombolytic administration, or (3) have shock likely to cause death within hours (before the onset of systemic thrombolytics).

xiii. Unless contraindicated, all patients should also receive a parenteral anticoagulant.
  (a) Intravenous unfractionated heparin is recommended over alternative agents for patients in whom thrombolytic therapy is being considered or planned.
  (b) The alteplase package insert recommends holding heparin during the alteplase infusion and reinstituting it when the aPTT returns to less than 2 times the upper limit of normal.
  (c) However, in some clinical trials, heparin was continued during thrombolytic administration.
  (d) Therefore, concurrent heparin administration with thrombolytic therapy in practice varies, and this decision should be individualized on the basis of risk assessment (e.g., bleeding vs. hemodynamics). If anticoagulation is contraindicated, an inferior vena cava filter should be placed.

D. A study highlighted the racial and socioeconomic disparities in the management and outcomes of acute PE in the United States. This study analyzed data from the Nationwide Inpatient Sample for 2016–2018 and identified 1,124,204 hospitalizations for acute PE among U.S. adults, with the disease of 66,570 patients (5.9%) classified as high risk. The study found that the hospitalization rate for PE increased across racial and ethnic groups, with Black people having the highest rate at 20.1 per 10,000 person-years, followed by White people at 13.1 per 10,000 person-years.

1. The authors reported that Black patients were 13% less likely to receive advanced PE therapy (thrombolysis, catheter-directed treatment, surgical embolectomy, or extracorporeal membrane oxygenation) than White patients (OR 0.87; 95% CI, 0.82–0.93; p<0.001), and Asian patients were 24% less likely than others (OR 0.76; 95% CI, 0.70–0.83; p<0.001). Patients with Medicare insurance were 27% less likely (OR 0.73; 95% CI, 0.70–0.76; p<0.001), Patients with Medicaid insurance were 32% less likely (OR 0.68; 95% CI, 0.64–0.71; p<0.001), and patients with "other-insurance" (including patients without insurance) were 14% less likely (OR 0.86; 95% CI 0.81–0.91; p<0.001) to receive advanced therapy than patients with private insurance.
2. With respect to mortality, Hispanic patients had a 10% higher mortality rate than White patients (OR 1.10; 95% CI, 1.03–1.18; p=0.005), and Asian patients had a 50% higher mortality rate than others (OR 1.50; 95% CI, 1.35–1.65; p<0.001). Patients with the lowest income also had a 9% greater mortality rate (OR 1.09; 95% CI, 1.04–1.14; p=0.001). Among patients with high-risk PE, Black, Hispanic, and Asian patients had an 11%–50% higher mortality rate than White patients, independent of other factors (p<0.05 for all racial/ethnic groups).

Patient Cases

7. A 48-year-old woman (weight 75 kg) presents to the ED with shortness of breath. The patient's hypoxemia does not improve with supplemental oxygen, and her chest radiograph is not significant for any lung abnormalities. A contrasted chest CT scan reveals a PE in the subsegmental branch of the right pulmonary artery and no RV dilation. The patient's vital signs and significant laboratory values are as follows: heart rate 118 beats/minute, blood pressure 98/62 mm Hg, urinary output 1 mL/kg/hour, troponin T 0.06 ng/mL, brain natriuretic peptide 60 pg/mL, lactate 0.9 mmol/L, and SCr 1.1 mg/dL. In addition to initiating a parenteral anticoagulant, which is best for the patient?

   A. Tenecteplase 40-mg bolus.
   B. Alteplase 100-mg infusion over 2 hours.
   C. Alteplase 50-mg bolus.
   D. No thrombolytic therapy.

8. A 56-year-old man (weight 140 kg) with a history of smoking and chronic obstructive pulmonary disease was admitted to the medical ICU with sudden-onset dyspnea, chest pain, and hypoxemia (Pa_{O_2} 78%). A chest CTA reveals a subsegmental PE. His blood pressure is 87/56 mm Hg, now requiring norepinephrine. Which is the next best step to evaluate and/or treat his PE?

   A. Administer tenecteplase 40-mg intravenous push, followed by a therapeutic heparin infusion.
   B. Obtain an echocardiogram and cardiac enzymes to guide further risk stratification.
   C. Administer catheter-directed alteplase 1 mg/hour for 12 hours by EKOS EndoWave system catheter.
   D. Administer alteplase 100 mg infused over 2 hours, followed by a therapeutic heparin infusion.

III. STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

A. Epidemiology

1. Severe cutaneous reactions and related syndromes are unpredictable and rare. The primary causes of these injuries include drugs, dysregulated immune response, and acute infection. Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN; also called Lyell syndrome), and drug hypersensitivity syndrome, or DRESS (drug rash with eosinophilia and systemic symptoms), are the most common presentations. There is a suggestion of genetic influence on the occurrence of SJS and TEN.
2. SJS and TEN are the most severe of reactions, representing different points on a similar spectrum of cutaneous injury involving epidermolysis or separation of the epidermis from the dermis.
3. Similar to thermal injury, the TBSA affected is used to describe the extent of cutaneous injury. According to contemporary reports from US burn centers, the mean TBSA involvement for patients with TEN is greater than 60%.
4. The incidence of severe cutaneous reactions is difficult to estimate. The highest rates reported approach 20%; however, definitions include mild to moderate reactions. The incidence of SJS and TEN is relatively low. SJS and TEN are considered rare diseases, with SJS occurring at a rate of about 1 to 2 cases per million people per year and TEN even less commonly, at about 0.4 to 1.2 cases per million people per year. Patients with HIV infection may have a higher incidence.
5. Severity of clinical presentation is associated with the extent of tissue and mucosal injury and necrosis. Most patients have a prodromal fever and malaise preceding cutaneous symptoms. Clinical presentation usually includes fever, systemic inflammatory response syndrome, hypotension from cytokine-mediated vasodilation, and mild to moderate hypovolemia from volume depletion and third spacing. Bleeding may also be present, depending on the extent of mucosal injury.
6. Health care–associated or nosocomial complications, including pneumonia, catheter-associated UTIs, central line–associated bloodstream infections, and malnutrition, are common in severely injured patients.
7. SJS and TEN are life-threatening reactions. Average crude mortality associated with SJS/TEN is 25% to 55% and can be as high as 90%.

B. Definitions

1. SJS and TEN are part of the same disease process, differing in severity. Common features of SJS and TEN include cutaneous erythema, progressive blistering, epidermolysis, and mucosal erosions.
2. The most widely accepted classification system for SJS and TEN was proposed in 1993. This system includes 5 categories:

Category	Epidermal detachment	Description
Bullous erythema multiforme	< 10% TBSA	Localized typical targets or raised atypical targets
SJS	< 10% TBSA	Widespread erythematous or purpuric macules or flat atypical targets
SJS/TEN overlap	10%-30% TBSA	Widespread purpuric macules or flat atypical targets
TEN with spots	> 30% TBSA	Widespread purpuric macules or flat atypical targets
TEN without spots	> 10% TBSA	Large sheets of epidermal detachment without purpuric macules or target lesions

C. Etiology
  1. Drugs are the most common cause of SJS and TEN and are implicated in more than 90% to 95% of cases. More than 200 medications have been reported as causing SJS and TEN. The most common agents implicated are sulfonamide antibiotics and aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine). Other agents/classes include:
    a. Abacavir
    b. Allopurinol
    c. β-Lactam antibiotics
    d. Lamotrigine
    e. Nevirapine
    f. NSAIDs, particularly the oxicams
    g. Quinolones, particularly ciprofloxacin
    h. Tetracyclines
  2. Vaccinations also have been associated with SJS and TEN, including MMR (measles, mumps, and rubella).
  3. Exposure to industrial chemicals and fumigants
  4. Infection with *Mycoplasma pneumoniae* can trigger SJS and TEN through a robust immune response and molecular mimicry, leading to widespread skin and mucosal cell damage.

D. Diagnosis
  1. Primary clinical signs/symptoms associated with SJS and TEN are fever and malaise, followed by cutaneous blisters and erosive mucosal lesions of the mouth, lips, eyes, and genital area. Distribution of cutaneous lesions is predominantly central, with mucosal involvement of usually at least 2 sites. Lesions consist of widespread, flat atypical targets or purpuric macules. TBSA is used to differentiate SJS from TEN and to categorize the severity of cutaneous and mucosal involvement. TBSA is calculated by the following:
    a. Arms—9% each
    b. Head and neck—9%
    c. Legs—18% each
    d. Perineum—1%
    e. Trunk—Anterior 18%; posterior 18%
  2. The diagnosis of SJS and TEN is confirmed by histopathologic analysis of lesional tissue and is corroborated with clinical presentation. Early lesions have scattered necrotic keratinocytes in the epidermis, whereas late-stage lesions have confluent full-thickness epidermal necrosis, which leads to the formation of subepidermal bullae.
    a. SCORTEN is a severity-of-illness system designed to predict mortality for TEN. It is computed within the first 24 hours of presentation and on day 3 using the sum of 7 objective clinical variables (each item present is worth 1 point):
      i. Age older than 40 years
      ii. Pulse rate greater than 120 beats/min
      iii. Presence of cancer or hematologic malignancy
      iv. Epidermal detachment greater than 10% TBSA on day 1
      v. Serum urea nitrogen greater than 28 mg/dL
      vi. Glucose greater than 252 mg/dL
      vii. HCO_3 less than 20 mEq/L
    b. Each of these parameters reflects the severity of the condition: Older age, high pulse rate, and underlying malignancies compromise recovery potential; extensive skin loss increases the risk of complications; and abnormalities in urea, HCO_3, and glucose indicate organ stress and metabolic disturbance, all of which correlate with increased mortality risk.

    c. Mortality prediction increases sharply with each additional point, starting at 3% for 0 or 1 point and reaching 90% for 5 or more points. SCORTEN mortality estimates are often used as benchmark rates to assess noncontrolled pharmacotherapy studies.

E. Management and Treatment
  1. Identification, discontinuation, and avoidance of likely or suspected causes are imperative. Causative agents with a long half-life should be identified and strategies to expedite removal considered.
  2. Transfer to the ICU, preferably at a certified burn center
  3. Overt assessment of mucous membranes to prevent extension of injury and related sequelae. This includes the respiratory tract, eyes, and GI tract.
  4. Cornerstones of managing SJS and TEN are:
    a. Resuscitation and supportive care (recent supportive care guidelines are outlined in *J Am Acad Dermatol.* 2020;82:1553-1567).
      i. Goal-directed fluid resuscitation should be initiated immediately to maintain:
        (a) MAP above 65 mm Hg
        (b) Central venous pressure 8 to 12 mm Hg
        (c) Urine output 0.5 to 1 mL/kg/h
        (d) Central venous oxygen saturation above 70%
      ii. Respiratory function should be supported with respiratory therapy and continual assessment for intubation, as appropriate.
      iii. Avoid using skin to anchor devices and catheters.
      iv. Physical and occupational therapy, when appropriate
    b. Limit debridement of necrotic epidermis. Best practice recommendations support leaving detached epidermis in place as a biologic dressing together with coverage of affected areas with an artificial or biologic dressing. This may be done serially because progression of affected areas may occur. Topical emollients (eg, petroleum jelly) should be applied to the entire epidermis.
    c. Management of extracutaneous injuries
      i. Ocular involvement
        (a) Adequate ocular lubrication
        (b) Consideration of topical, preservative-free ophthalmic corticosteroid drops
        (c) Treatment of corneal fluorescein or ulceration
      ii. Oral involvement
        (a) Maintain lip barrier integrity (eg, white paraffin).
        (b) Consider antiseptic oral rinse (eg, chlorhexidine).
        (c) Consider topical corticosteroid rinse (eg, betamethasone).
    d. Nutrition support (see Fluids, Electrolytes, Acid-Base Disorders, and Nutrition Support chapter)
    e. Avoidance and treatment of infectious complications
      i. Implement infection prevention best practices, including minimizing unnecessary devices and procedures related to health care–associated infection.
      ii. Prophylactic antibiotic therapy is not recommended for SJS and TEN.
      iii. Empiric antibiotic therapy should be carefully chosen and reserved for suspected infections, as evidenced by signs and symptoms of sepsis or site-specific infection. Continuation of antibiotic therapy should be reserved for confirmed infection, and duration should be limited according to the specific infection.
  5. Adjuvant therapies
    a. Plasmapheresis—Support is derived from case series; thought to be a generally safe and effective strategy to remove pathogenic, nondialyzable plasma factors, including some drugs, toxins, metabolites, antibodies, immune complexes, and disease-inducing cytokines

b. Immunomodulating therapy
    i. Corticosteroids—Despite some evidence of benefit, use is controversial and not universally recommended. More recent case reports suggest that high-dose pulse therapy during the first 3 days of presentation decreases disease progression. Associated risks (eg, infection; hyperglycemia, poor wound healing) may outweigh benefits.
        (a) A 2009 study examined the efficacy of early intervention with steroid pulse therapy in patients with SJS and TEN, specifically focusing on ocular outcomes (*Am J Ophthalmol.* 2009;147(6):1004-1011.e1). This prospective observational case series enrolled 5 patients with SJS or TEN who presented with ocular complications during the acute stage of the disease between May 2003 and June 2005 at Kyoto Prefectural University of Medicine, Japan. The treatment regimen included intravenous pulse therapy with methylprednisolone (500 or 1000 mg/d for 3 or 4 days) initiated within 4 days of disease onset, supplemented by topical applications of 0.1% betamethasone more than five times daily for at least 2 weeks. The study found significant improvements in skin eruptions after the steroid pulse therapy, and although ocular inflammation initially increased, it subsided with the disappearance of pseudomembranes and regeneration of corneal and conjunctival epithelium within 6 weeks. One year from onset, all treated eyes exhibited clear corneas with visible palisades of Vogt, suggesting preservation of corneal epithelial stem cells. Best-corrected visual acuity (BCVA) was 20/20 or better in all eyes, with only minor complications such as superficial punctate keratopathy and slight fornix shortening in 1 eye. No significant adverse effects from the steroids were observed. The study concluded that early steroid pulse therapy combined with topical betamethasone is crucial in preventing severe ocular complications and preserving corneal health in patients with SJS and TEN.
        (b) A 2008 study investigated the impact of various treatments on mortality rates in patients with SJS and TEN (*J Am Acad Dermatol.* 2008;58(1):33-40). This retrospective analysis was part of the EuroSCAR study, a larger prospective case-control study evaluating risk factors involving patients from France and Germany. The study specifically examined the effectiveness of intravenous immunoglobulin (IVIG) and corticosteroids compared with supportive care alone. The results indicated that neither IVIG nor corticosteroids significantly affected mortality rates compared with supportive care. Specifically, the odds ratios for death with IVIG were 1.4 in France and 1.5 in Germany, whereas odds ratios for death with corticosteroids were 0.4 in France and 0.3 in Germany, none of which showed significant differences. The study highlighted the limitations inherent in such observational studies, such as data collection variability, heterogeneity in supportive care practices, and differences in treatment approaches across countries. Ultimately, the study concluded that evidence was insufficient to recommend any specific treatment for reducing mortality in SJS and TEN. However, the data suggested a potential beneficial trend for corticosteroids that could warrant further investigation.
        (c) Investigators of a subsequent study conducted a comprehensive survival analysis of a cohort of patients with SJS and TEN as part of the RegiSCAR study (*J Invest Dermatol.* 2013;133(5):1197-1204). This research aimed to assess risk factors for mortality, including patient treatment modalities, up to 1 year after the reaction. In patients for whom treatment details were available (n = 442), there was no observed benefit or harm with corticosteroids (HR, 1.3; 95% CI, 0.8-1.9).
        (d) A 2017 meta-analysis using individual data from 1209 patients, of whom 367 received systemic corticosteroids in addition to supportive treatment, found that corticosteroid treatment was associated with a modestly decreased risk of death compared with supportive treatment alone (OR, 0.67; 95% CI, 0.46-0.97).

ii. Cyclosporine—Information from individual case series suggests benefit at a dose of 3 mg/kg/d. There are no formal recommendations for routine use.

iii. Cyclophosphamide—Early case reports suggested benefit, but cyclophosphamide is not recommended.

iv. Colony-stimulating factor—May be used in conjunction with cyclosporine in patients with neutropenia and TEN

v. IVIG

   (a) IVIG for SJS and TEN is controversial.

   (b) In vitro data support that immunoglobulin G antibodies against Fas-FasL proteins may decrease keratinocyte apoptosis.

   (c) Many retrospective single-group and cohort studies suggest benefit (usual dosage, 1 g/kg/d for 3 days) over SCORTEN-estimated mortality rates and similar control groups, respectively.

   (d) Given the rare incidence and logistical difficulty of designing a multicenter prospective study, available prospective studies have been small and single center. Results from these studies, however, have shown no benefit to trends of worse outcomes.

   (e) A 2015 study examining the impact of early systemic immunomodulatory treatment identified prognostic factors for chronic ocular complications in patients with SJS and TEN (*Ophthalmology.* 2015;122(2):254-264). Conducted as a retrospective, comparative, multicenter study across 3 university hospitals in Korea, it included 43 patients diagnosed with SJS or TEN. The treatments were categorized into 5 groups: systemic steroids, IVIG, combined steroids and IVIG, systemic pulse steroids, and supportive care only. The study measured outcomes according to BCVA and chronic ocular surface complications score (COCS) at the final follow-up. Despite the varied treatments, there were no significant differences in final BCVA and COCS between the groups after adjusting statistically. High COCS was notably associated with female sex and the use of amniotic membrane transplantation during the acute stage. In addition, severe acute ocular and systemic involvement scores were linked to worse COCS, which correlated strongly with final BCVA. The study concluded that systemic immunomodulatory treatments did not significantly affect the final visual outcomes or COCS in patients, indicating that factors such as sex and the severity of initial symptoms may be more critical in predicting long-term ocular complications in SJS and TEN.

   (f) A 2005 study focused on the efficacy of high-dose IVIG in reducing acute ocular complications in patients with TEN (*Eye (Lond).* 2005;19(8):846-853). This retrospective, historically controlled study compared 10 consecutive patients treated with high-dose IVIG at Tan Tock Seng Hospital, Singapore, from July 2001 to June 2002, against 18 historical cohort patients diagnosed with TEN between July 1995 and June 2001 who did not receive IVIG. The treated group received 2 g/kg of IVIG over 2 days. The analysis showed that 90% of the patients treated with IVIG experienced ocular involvement, with varying severity: mild complications like lid edema or mild conjunctival injection in 25%, moderate complications such as pseudomembranes in 50%, and severe complications including nonhealing epithelial defects with visual loss and symblepharon in 25%. In contrast, 55.6% of the historical cohort experienced ocular issues, predominantly mild to moderate, with no severe cases reported. The study concluded that IVIG treatment did not significantly reduce the severity of visually significant ocular complications in patients with TEN, suggesting a need for larger studies to confirm these findings.

   (g) A systematic review and meta-analysis of use in patients with TEN found no benefit over standard of care.

(h) The decision to administer IVIG remains clinically supported by pathophysiology-pharmacology interactions and observational data. Centers with expertise to care for patients with TEN should assess the usefulness of IVIG and develop interdisciplinary guidance for local use.

vi. Consensus guidelines from the United Kingdom recommend that immunomodulating therapies be used under the supervision of skin failure specialists in the context of a clinical study or registry. In contrast, consensus guidelines from India recommend (grade B recommendation) that low-dose IVIG be considered in the first 24 to 48 hours in patients with HIV, children, and pregnant women in the first trimester.

Patient Case

Questions 9 and 10 pertain to the following case.
L.H. is a 23-year-old woman diagnosed with an uncomplicated UTI. Two days after starting sulfamethoxazole-trimethoprim, she presents to the burn ICU from an outside hospital with severe systemic inflammatory response and 30% TBSA epidermolysis of her upper arms and back. Six hours earlier, she had only 10% TBSA involvement. During her stay in the burn ICU, new lesions develop on her thighs and oral cavity, increasing TBSA involvement to 40%, consistent with TEN. L.H.'s SCORTEN score is 3.

9. Which is the most appropriate initial pharmacotherapeutic intervention for L.H.?
   A. Crystalloid resuscitation.
   B. Cyclophosphamide.
   C. Empiric vancomycin for wound prophylaxis.
   D. High-dose systemic corticosteroids.

10. Given L.H.'s worsening condition with TBSA involvement now at 50%, progressing oral cavity injury, and acute kidney injury, you and your team consider IVIG as a pharmacotherapeutic intervention. Which best reflects the evidence-based role of IVIG in managing TEN?
    A. IVIG should be administered before the patient's condition progresses to TEN.
    B. IVIG should be reserved for specialty centers with interdisciplinary consensus protocols to guide use.
    C. Multicenter pivotal trials show that IVIG is most efficacious for patients with ocular involvement.
    D. Meta-analyses of the available evidence support that IVIG is standard of care in managing TEN.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

This patient has class II hemorrhagic shock caused by penetrating trauma (heart rate greater than 100 beats/minute, respiratory rate 20–30 breaths/minute, and anxious on examination). The appropriate resuscitation strategy should focus on selecting the fluid, volume, and resuscitation goal. Recommended end points for resuscitation include SBP greater than 90 mm Hg, urinary output greater than 30 mL/hour, and normal mentation. Administering fluid to target an SBP greater than 90 mm Hg would be appropriate (Answer A is incorrect). Blood products for transfusion are indicated when the patient's estimated blood loss is greater than 30% (Answers B and C are incorrect because the patient has class II hemorrhagic shock). Given his hemorrhagic shock class, the patient may be initially managed with crystalloid boluses targeting a urinary output greater than 30 mL/hour, an SBP greater than 90 mm Hg, and normal mentation (Answer D is correct).

2. **Answer: B**

Using the Parkland formula for burn resuscitation, the 24-hour fluid requirement would be 13.6 L, to be segmented into the first 8 hours of resuscitation and the remaining 16 hours. Calculating fluid requirements according to weight and TBSA to target a urinary output of greater than 0.5 mL/kg/hour would be correct (Answers A, C, and D are incorrect). Answer B is correct because the total volume requirement accounting for prehospital fluid, titration of fluid rates, and target urinary output are appropriate.

3. **Answer: D**

Given this patient's hemodynamic parameters in a positive FAST examination, he will likely require a massive transfusion, as assessed by the ABC (Assessments of Blood Consumption) score for an MTP, which should be initiated promptly. A fixed ratio of 1:1:1 PRBC, plasma, and platelets is more likely to achieve hemostasis and lower mortality from exsanguination at 24 hours than is 2:1:1 (Answer D is correct). Although fluid resuscitation is an adjunct to increase intravascular volume and tissue perfusion, 0.9% sodium chloride does not increase oxygen-carrying capacity, and total volume should be minimized to less than 1.5 L (Answer A is incorrect). In a traumatic hemorrhage, a normal hemoglobin likely will not reflect the extent of blood loss secondary to hemoconcentration until capillary recruitment is complete or resuscitation begins. In addition, resuscitation efforts in a hemodynamically unstable patients should not be delayed while awaiting laboratory results (Answer B is incorrect). Although vasopressors may be considered an adjunct to maintain tissue perfusion while minimizing fluid volume, this strategy should be reserved for those with life-threatening hypotension despite resuscitation efforts (Answer C is incorrect).

4. **Answer: B**

Acute hypocalcaemia is a common complication in a massive transfusion secondary to citrate added to stored blood. Calcium is essential for stabilization of fibrin, and low ionized calcium concentrations in traumatic hemorrhage are associated with increased mortality. Therefore, ionized calcium concentrations should be maintained within the normal range (Answer B is correct). Evidence is insufficient to recommend sodium bicarbonate therapy in patients with acute trauma and has the potential for increased mortality. The patient's acidosis should be corrected by addressing the underlying cause – in this case, hemorrhage (Answer A is incorrect). Use of rFVIIa should only be considered if major bleeding and persistent traumatic coagulopathy persist despite best practice, inconsistent with the patient's current condition. In addition, a pH less than 7.2 is a predictor of a poor response to rFVIIa (Answer C is incorrect). Unfortunately, this patient's injury was 5 hours ago, and he has no laboratory evidence of hyperfibrinolysis. In this setting, tranexamic acid does not improve mortality after 3 hours from injury and has been associated with an increased risk of death from bleeding (Answer D is incorrect).

5. **Answer: C**

At this point, ongoing resuscitation should be goal directed. The TEG reveals hypofibrinolysis or "shutdown," not hyperfibrinolysis for which tranexamic acid is expected to help. In addition, if there was no TEG to evaluate for hypofibrinolysis, tranexamic acid should be administered within the first 3 hours from injury, and this patient's injuries occurred more than 4 hours earlier (Answers B and D are incorrect). With the updated history that the patient was taking dabigatran preinjury, dabigatran is likely contributing to the patient's ongoing coagulopathy and hemorrhage.

A normal TEG and elevated aPTT may not rule out the presence of dabigatran. In addition, it seems the patient took the last dabigatran dose within the previous 12 hours. Therefore, dabigatran reversal is indicated. Idarucizumab is FDA approved for dabigatran reversal and recommended in various guidelines, whereas PCCs have weak supporting evidence and are recommended only if idarucizumab is unavailable (Answer C is correct; Answer A is incorrect).

6. **Answer: B**

This patient has an acute GI hemorrhage complicated by supratherapeutic INR warfarin and hemodynamic instability necessitating warfarin reversal with 4F-PCC. Given his weight and degree of INR elevation, the package insert dose is 50 units/kg not to exceed 5000 units (Answer B is correct; Answer D is incorrect). Although fixed, low-dose PCC has been evaluated for warfarin reversal, this dose is off-label and supported by a lower quality of evidence. In addition, the 1000-unit dose has shown lower achievement of a goal INR, necessitating rescue doses, and a low dose would probably not achieve adequate laboratory reversal, given his weight and excessively high INR (Answer A is incorrect). Finally, although rFVIIa lowers INR, it is no longer recommended for the reversal of vitamin K antagonists, given the incomplete correction of factors II, IX, and X and the possibility that the INR does not reflect the patient's underlying coagulopathy (Answer C is incorrect).

7. **Answer: D**

The patient has evidence of a PE, but she lacks features of an increased risk of early mortality from it. She does not have shock or evidence of end-organ hypoperfusion and thus does not have a massive PE. In addition, she has no evidence of RV dysfunction (no RV dilation on chest CT, brain natriuretic peptide less than 90 pg/mL) or myocardial necrosis (troponin less than 0.1 mg/mL) and thus does not have a submassive PE. The patient is best classified as having a low-risk PE. A meta-analysis suggested that thrombolytics do not decrease mortality in unselected (and low risk) patients and may increase bleeding risk (Answer D is correct; Answers A–C are incorrect).

8. **Answer: D**

The patient has a massive or high-risk PE, as evidenced by signs of hemodynamic complications requiring norepinephrine, likely confounded by poor physiologic reserve with chronic obstructive pulmonary disease. The current guidelines recommend systemic thrombolysis in patients with a massive PE and an acceptable risk of bleeding. This patient does not appear to have any obvious risk of bleeding, including age; therefore, systemic thrombolytic agents are indicated in addition to a therapeutic heparin infusion. The most common options include alteplase as a fixed dose of 100 mg infused over 2 hours or tenecteplase adjusted according to patient weight. Because this patient weighs 140 kg, the recommended tenecteplase dose would be a 50-mg intravenous push once (Answer A is incorrect); therefore, alteplase 100 mg infused over 2 hours is the most appropriate answer (Answer D is correct). The 2021 CHEST guidelines state that if thrombolytic agents are indicated, systemic thrombolysis is preferred to catheter-directed thrombolytic administration (Answer C is incorrect). Echocardiogram and cardiac enzymes are not considered necessary to guide therapy in patients with hypotension/shock and a CTA-confirmed PE (Answer B is incorrect).

9. **Answer: A**

One of the cornerstones of managing severe cutaneous injury includes volume resuscitation, preferentially with crystalloids (Answer A is correct). The usefulness of immunomodulating therapies such as corticosteroids and cyclophosphamide is limited by observational and poorly controlled evidence or case reports; thus, use of immunomodulating therapies should be reserved for specialty centers using formal protocols with consideration for treatment under clinical study or registry (Answers B and D are incorrect). Wound care is imperative in these patients; however, adding unnecessary drugs that could confound response or worsen the injury (eg, antibiotics) should be avoided (Answer C is incorrect) unless there is an objectively suspected or confirmed infection.

10. **Answer: B**

Use of IVIG for SJS/TEN is controversial. Available evidence is from case reports/series, observational cohort studies, or small, single-center randomized trials (Answer C is incorrect). Because of bias, limited external validity, and mixed results/observations between publications, meta-analyses and consensus guidelines do not broadly endorse the use of IVIG (Answer D is incorrect). Available data analyses suggest that IVIG decreases the SCORTEN-related mortality in patients with TEN and a middle to higher SCORTEN score; there are even fewer data for the role of IVIG in SJS (Answer A is incorrect). Given the limited evidence supporting pharmacotherapeutic interventions and the life-threatening severity of TEN, burn referral centers should base the decision to use IVIG on local protocols/guidelines developed by interdisciplinary practitioners who have objectively evaluated the available evidence regarding safety, efficacy, and pharmacogenomic implications (Answer B is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

This patient presents with likely hemorrhagic shock after blunt trauma. The extent of injuries in highly vascularized areas suggests a hemorrhagic source. Given the extent of confusion, oliguria, tachycardia, and tachypnea, as well as the amount of blood loss (35% of total blood volume), this patient has class III hemorrhage (Answer C is correct; Answers A, B, and D are incorrect).

2. **Answer: C**

The Fick equation describes oxygen delivery (Do_2 (mL/minute) = 10 x CO (L/minute) x Cao_2). A diagnosis of shock is typically based on hemodynamic, clinical, and biochemical assessment of impaired Do_2. Although an elevated INR may represent a coagulopathy that can contribute to bleeding, it is not directly related to impaired Do_2. In addition, hematemesis is a clinical sign of bleeding but is not necessarily specific to a shock syndrome (Answer A is incorrect). Although heart rate is a determinant of CO, CO is not generally impaired unless the patient has acute supraventricular or ventricular tachycardia. In addition, an elevated serum creatinine may be a biochemical sign of impaired tissue oxygenation, but this generally presents in a delayed fashion and may represent chronic renal dysfunction in this specific patient (Answer B is incorrect). A low $Scvo_2$ represents the balance between oxygen consumption and delivery (not solely delivery) and does not explain reduced Do_2. Although an elevated lactate concentration may indicate impaired Do_2 in shock syndrome, lactate may be elevated secondary to altered hepatic metabolism and is not a specific marker for circulatory shock (Answer D is incorrect). Therefore, according to the Fick equation, a low hemoglobin reduces the Cao_2, decreasing Do_2. Cold and clammy extremities is a common clinical marker of a shock syndrome, indicating a low-flow state (Answer C is correct).

3. **Answer: D**

This patient presents with likely hemorrhagic shock after blunt trauma. The patient has signs consistent with intra-abdominal bleeding with the positive FAST examination in hemodynamic instability; thus, urgent intervention is required. According to the extent of altered mentation, tachycardia, and tachypnea, this patient has class IV hemorrhage, consistent with greater than 40% blood loss, indicating the requirement for erythrocyte transfusions. However, giving only erythrocyte transfusions would increase oxygen-carrying capacity but not correct the likely underlying coagulopathy (Answer A is incorrect). Although warmed lactated Ringer solution may be indicated in a trauma patient with bleeding, excessive fluid resuscitation (above 1.5 L) should initially be avoided (Answer B is incorrect). Given the patient's blood pressure, heart rate, and positive FAST, he is at high risk of requiring massive transfusion, which should be initiated promptly with an empiric ratio. In addition, given the presence of hemorrhagic shock requiring erythrocyte transfusions, tranexamic acid is indicated early to improve mortality (Answer D is correct). Although goal-directed resuscitation is recommended for continued resuscitation, empiric blood product transfusions should not be delayed while awaiting laboratory results unless point-of-care assays are available (Answer C is incorrect).

4. **Answer: B**

This patient has apparent warfarin toxicity contributing to an acute GI hemorrhage. Because he meets the criteria for a major bleed, particularly associated with hemodynamic instability, many guidelines recommend anticoagulation reversal. Although phytonadione is the specific reversal for warfarin to promote hepatic production of factors II, VII, IX, and X, it does not immediately correct coagulopathy, and factor replacement is recommended (Answer D is incorrect). In addition, when used for life-threatening hemorrhage, intravenous administration is recommended because of its quicker onset of action of 4–6 hours compared with 18–24 hours for oral administration (Answer A is incorrect). Although plasma has traditionally been used for immediate factor replacement for warfarin reversal, the time to laboratory reversal is inferior to PCC. In addition, the volume of plasma needed to reverse his INR would likely not be well tolerated by this patient with CTEPH (Answer C is incorrect). Therefore, 4F-PCC, which contains nonactivated highly concentrated factors II, VII, IX, and X, is recommended for warfarin reversal in life-threatening hemorrhage because of its superiority for laboratory reversal and noninferiority for clinical hemostasis. Rates of thrombotic events appear similar when comparing 4F-PCC with plasma for warfarin reversal in life-threatening hemorrhage and surgical populations; however, rates of fluid overload complications are greater with plasma (Answer B is correct).

5. **Answer: A**

The patient has a massive PE, as evidenced by pulseless activity. Massive PE should be treated with thrombolytic therapy unless absolute contraindications to thrombolytics are present. Prolonged chest compressions may be considered a relative contraindication to thrombolytics, but this patient had a short duration of chest compressions (Answer A is correct). Troponin T and brain natriuretic concentrations may help classify a patient as having a submassive PE, but the patient in this case has already fulfilled the criteria for a massive PE, and these laboratory values will not change the patient's treatment (Answers B and C are incorrect). Although a TTE might provide information on RV function, it is unlikely to change the patient's treatment plan with thrombolytics and might delay therapy (Answer D is incorrect).

6. **Answer: B**

This patient's PE is causing stress on the RV, as evidenced by his echocardiogram and positive cardiac enzymes. Therefore, this is not a low-risk PE (Answer D is incorrect). However, the patient is hemodynamically stable at this point, so it is also not a high-risk PE (Answer A is incorrect). Given that the patient has both evidence for RV straining and myocardial ischemia as represented by both the echocardiogram and the cardiac enzymes, this meets the criteria for an intermediate-high risk PE (Answer B is correct; Answer C is incorrect).

7. **Answer: B**

This patient appears to be clinically worsening with blood pressures that are approaching hemodynamic instability and worsening oxygenation requiring high levels of $\mathrm{F_{IO_2}}$. Consideration for reperfusion therapy is warranted. Given his history of a recent GI bleed requiring ICU admission, systemic, full-dose thrombolytics would be contraindicated (Answer A is incorrect). A thrombolytic strategy to minimize the risk of bleeding may be appropriate. Although half-dose alteplase has been studied, it is not recommended because of insufficient evidence (Answer C is incorrect). Therefore, in intermediate-high risk PE with clinical deterioration, the guidelines recommend CDT when systemic thrombolytic contraindications exist and resources are available, such as in an urban, academic ICU. Catheter-directed thrombolysis is administered with mechanical methods (e.g., ultrasound-assisted thrombolysis) and specific catheters (not pulmonary artery catheters) (Answer B is correct; Answer D is incorrect).

8. **Answer: A**

This patient now has a cardiac arrest secondary to his PE. Because he has a confirmed PE as the precipitant of cardiac arrest, systemic thrombolytic is recommended as an emergency treatment. Given the mortality rates from PE in a cardiac arrest, standard contraindications to thrombolysis may be suspended in favor of a lifesaving intervention. Systemic thrombolytics in this setting may be associated with return of spontaneous circulation and possibly survival benefits (Answer D is incorrect). The recommended alteplase dose is a 50-mg intravenous bolus, repeated in 15 minutes if needed (Answer A is correct; Answer C is incorrect). Although surgical embolectomy would be reasonable in the operating room, systemic thrombolytics would be preferred, given the patient's current location in the ICU (Answer B is incorrect).

9. **Answer: D**

This patient is experiencing a high-risk or massive PE, as evidenced by a confirmed CT scan, clinical signs consistent with a PE, and a dilated right ventricle on TTE in the setting of sustained hypotension requiring norepinephrine. Although an inferior vena cava filter may prevent additional embolization, it will not limit the growth or cause lysis of the current clot burden associated with his PE (Answer A is incorrect). For a high-risk or massive PE, administration of systemic thrombolytic agents is recommended unless contraindications are present. Because this patient had a recent subarachnoid hemorrhage, the risk of systemic thrombolytic therapy might outweigh the potential benefit (Answer B is incorrect), even at a reduced dose (Answer C is incorrect). Therefore, the CHEST guidelines recommend CDT for patients who are hemodynamically unstable from a PE but have a high bleeding risk (Answer D is correct).

Pain, Agitation/Sedation, Delirium, Immobility, Sleep Disruption, and Neuromuscular Blockade

Joanna L. Stollings, Pharm.D., FCCP, FCCM, BCPS, BCCCP

Vanderbilt University Medical Center
Nashville, Tennessee

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Joanna L. Stollings, Pharm.D., FCCP, FCCM, BCPS, BCCCP

Vanderbilt University Medical Center
Nashville, Tennessee

Learning Objectives

1. Develop a management strategy for the prevention and treatment of pain, agitation/sedation, and delirium, immobility, and sleep disruption (PADIS) in an intensive care unit (ICU) patient with various comorbidities.
2. Discuss relevant pharmacokinetic and pharmacodynamic considerations of PADIS medications as they pertain to disturbances in critical care physiology.
3. Identify relevant adverse effects, drug interactions, and drug withdrawal syndromes in the management of PADIS.
4. Evaluate patients in the ICU for PADIS using a validated screening tool.
5. Construct a plan for the management of delirium.
6. Identify the long-term effects of critical illness in adult ICU patients.
7. Create a management strategy for PADIS-related medications that are continued beyond ICU discharge.
8. Describe a treatment and monitoring plan for critically ill patients receiving neuromuscular blockade.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
BPS	Behavioral Pain Scale
CAM-ICU	Confusion assessment method for the intensive care unit
CPOT	Critical-Care Pain Observation Tool
GABA	γ-Aminobutyric acid
ICDSC	Intensive Care Delirium Screening Checklist
ICP	Intracranial pressure
ICU	Intensive care unit
NMBA	Neuromuscular blocking agent
PAD	Pain, agitation, and delirium
PADIS	Pain, agitation/sedation, delirium, immobility, and sleep disruption
PRIS	Propofol-related infusion syndrome
RASS	Richmond Agitation Sedation Scale
SAS	Sedation-Agitation Scale
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine
TOF	Train of four

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. P.J. has been receiving propofol 50–60 mcg/kg/minute and fentanyl 75–100 mcg/hour for 4 days. She has no significant medical history. Laboratory results today show that transaminases have increased to 5 times baseline, lactate is increased to 5 mmol/L, and triglyceride concentration is 450 mg/dL. No new medications have been added. Given these laboratory values, which complication would be most appropriate to address?
   - A. Deep venous thrombosis (DVT).
   - B. Critical illness-induced polyneuropathy.
   - C. Intensive care unit (ICU) delirium.
   - D. Propofol-related infusion syndrome (PRIS).

2. T.I. is a 35-year-old man admitted to the ICU for severe alcohol withdrawal. His medical history is otherwise unknown. Laboratory values are within normal limits on admission. He has been receiving a lorazepam infusion 6–8 mg/hour for active alcohol withdrawal. On day 4, his blood pressure is 130/75 mm Hg, oxygen saturation is 98% on 2 L of oxygen, blood urea nitrogen (BUN) is 50 mg/dL, and serum creatinine (SCr) is 2.0 mg/dL; he has a new anion gap of 20 mEq/L, an osmolar gap of 18 mmol/L H_2O, and a fractional excretion of sodium of 0.2. Which is the most likely cause for his clinical presentation?
   - A. Acute respiratory distress syndrome (ARDS).
   - B. Propylene glycol toxicity.
   - C. Delirium tremens.
   - D. Acute tubular necrosis.

3. R.B. is a 25-year-old man admitted to the ICU for acute pancreatitis and sepsis. He is intermittently agitated on hydromorphone 2 mg/hour and midazolam 6 mg/hour (Richmond Agitation-Sedation Scale [RASS] score of –1 to +2) and is not oxygenating adequately after adjustments on the ventilator. The physician would like to initiate therapeutic paralysis. Which is the next best step in the treatment of this patient?

A. Spontaneous awakening and breathing trials.
B. Cisatracurium infusion.
C. Intermittent vecuronium.
D. Sedate the patient to a "deeply sedated" clinical state.

4. P.V. is a 70-year-old woman (weight 50 kg, decreased from 60 kg 2 months ago) admitted to the ICU in ARDS. She has a history of cirrhosis and is currently fluid overloaded (net positive 5 L). She has been on a continuous infusion of fentanyl and propofol for 5 days. Which pharmacologic factor would best be considered with respect to her analgesics or sedatives?

A. Risk of PRIS in patients with ARDS.
B. Unpredictable clearance of fentanyl.
C. Enzymatic induction of fentanyl by propofol.
D. Hypocalcaemia secondary to extended use of propofol.

5. L.B. is a 38-year-old woman intubated in the neurosurgery ICU for 72 hours receiving propofol. The nurse is requesting medications for "severe agitation and hallucinations." Her heart rate and blood pressure have steadily increased since admission, and a chart review reveals years of chronic pain while receiving oxycodone and tramadol at home. Her laboratory values are normal, but she is not tolerating enteral-route medications. Which is the most appropriate recommendation at this time?

A. Quetiapine as needed for agitation.
B. Fentanyl infusion.
C. Lorazepam as needed for agitation.
D. Hydromorphone patient-controlled analgesia.

6. S.P. has just been intubated in the ICU and is in severe alcohol withdrawal. He has a history of frequent delirium tremens and alcohol withdrawal seizures. Which medication is most appropriate to begin initial management of pain, agitation, and delirium (PAD) in this patient?

A. Dexmedetomidine.
B. Phenytoin.
C. Fentanyl.
D. Midazolam.

7. H.F., a 65-year-old man admitted to the ICU from home for aspiration pneumonia requiring intubation, is initiated on levofloxacin and metronidazole. Other medications include fentanyl and dexmedetomidine infusions as well as amiodarone, a home medication. His last RASS was -2, and he has intermittent agitation. Vital signs and laboratory values are normal, and corrected QT (QTc) is 550 milliseconds. Which is the most appropriate recommendation at this time?

A. Add quetiapine for agitation, and monitor QTc.
B. Start nonpharmacologic management of agitation/delirium.
C. Discontinue dexmedetomidine because of his prolonged QTc.
D. Give lorazepam as needed for agitation.

8. S.V., a 70-year-old woman with a history of hypertension, is transferred from the floor to the ICU for worsening pneumonia and new-onset hypoactive delirium. She has been nil per os (NPO) since admission 3 days prior. She remains febrile (temperature 102°F [38.89°C]) with decreased urine output; other vital signs and laboratory values are within normal limits. Her medications include ceftriaxone, heparin, and hydrochlorothiazide. Which best represents the most important set of considerations regarding her delirium?

A. Dementia and sleep disorder.
B. Undetected alcohol withdrawal.
C. Adrenal insufficiency.
D. Dehydration and untreated infection.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1 -5
    b. Task B: 2
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1 -6
    b. Task B: 1, 4, 13, 14, 16
    c. Task C: 1, 4
3. Domain 3: Professional Practice
    a. Task A: 4
    b. Task B: 1, 4, 6

I. PAIN, AGITATION/SEDATION, DELIRIUM, IMMOBILITY, AND SLEEP DISRUPTION (PADIS) IN THE INTENSIVE CARE UNIT

A. Background
   1. The Society of Critical Care Medicine (SCCM) published updated guidelines for the management of PADIS in adult ICU patients in 2018 (Crit Care Med 2018;46:e825-e873). These guidelines, together with recently published research, help guide ICU clinicians in the challenging task of optimizing patient comfort and outcomes while avoiding the complications of under- or oversedation. The PADIS guidelines were written by 32 international experts, four methodologists, and four critical illness survivors who met virtually monthly and annually at annual SCCM congresses. Rigorous research has developed our understanding of the assessment tools and medications used for PADIS, the prevention and treatment methods used for PADIS, and the long-term effects of the ICU environment on patients and caregivers. Recommendations for specific ICU populations such as burn, neurologic, neurosurgical (including traumatic brain injury), and cardiac populations may need specialized consideration.
   2. The PADIS guidelines add to the 2013 pain, agitation, and delirium (PAD) guidelines by:
      a. Adding two critical care topics: rehabilitation/mobilization and sleep disruption
      b. Including patients as collaborators and coauthors
      c. Inviting an international panel of experts from high-income countries to incorporate more diverse practices and expertise from the global critical care community
   3. Each section of the 2018 PADIS guidelines was represented by content experts, methodologists, and ICU survivors. Population, Intervention, Comparison, and Outcome and nonactionable descriptive questions were developed by each section. Members of the guideline group voted on their ranking, and patients voted on their perceived importance. According to the Grading of Recommendations Assessment, Development, and Evaluation principles, every Population, Intervention, Comparison, and Outcomes question was evaluated by members of each section to determine the best level of evidence, assess quality, and determine recommendations as “strong,” “conditional,” or “good” practice. Evidence gaps and clinical caveats were explicitly identified.

B. Pharmacy Intervention – Pharmacists provide unique and valuable insight into the management of PADIS in the ICU. Much of the management for PADIS involves medications with complex pharmacologic profiles, allowing many opportunities for pharmacy expertise on the critical care team. As the management of PADIS in the ICU continues to evolve, pharmacists should seek avenues for contributing to the critical care community through development of hospital protocols and assessing for quality improvement; providing education for medical, pharmacy, and nursing colleagues; and/or doing research on pertinent questions surrounding the management of PADIS in the ICU (Crit Care Med. 2020;48:e813-e834).

II. PAIN IN THE INTENSIVE CARE UNIT

A. Introduction
   1. More than half of ICU survivors report severe pain as the most traumatic memory of their ICU stay.
   2. Both short- and long-term negative sequelae are related to uncontrolled pain in the ICU. Assessing pain in the ICU is challenging, particularly in patients who cannot effectively communicate. If patients cannot adequately communicate their degree of pain but retain motor activity, medications should be titrated according to validated behavioral pain scales.

B. Incidence and Causes of Pain: Pain may occur in any type of ICU patient, and considerations for pain management often require an individualized approach to optimize treatment. The interdisciplinary team should complete a comprehensive review of all variables such as acute and chronic pain, routine nursing care that may cause discomfort, and procedural-based pain.
   1. Common causes of pain in the ICU include, but are not limited to, acute trauma, injury or burns, postoperative pain, exacerbation of chronic pain, heart disease, ischemia, acute or chronic underlying disease state pain such as cancer pain, pancreatitis, or other abdominal pathology.
   2. Less discernible causes of pain may include those from either routine nursing care or the provision of life-sustaining measures: presence of an endotracheal tube and endotracheal tube suctioning, wound care, tube or Foley insertion, immobility, bed repositioning, bathing, medication administration, and physical and occupational therapy. Other examples of painful invasive procedures include intravenous line placement, endoscopy and bronchoscopy, chest tube placement or removal, paracentesis, lumbar puncture, biopsies, and fracture reductions.

C. Short- and Long-term Consequences of Pain in the ICU
   1. Acute pain can invoke a stress response, resulting in a hypercatabolic state, decreased tissue perfusion, and impaired wound healing. Uncontrolled pain decreases a patient's immune response to infection by suppressing natural killer cell activity and neutrophil function.
   2. Long-term studies (12 months post-ICU stay) report detrimental physiologic and psychological function in patients who recall significant pain during their hospitalization, particularly in patients admitted with a traumatic injury (Lancet Respir Med 2014;2:369-79).
      a. Health-related quality of life is decreased in up to 20% of patients.
      b. Chronic pain is reported in up to 40% of patients.
      c. Posttraumatic stress disorder is reported in 5%–20% of patients.

D. Assessment of Pain
   1. The gold standard for assessing pain remains the patient's self-report of pain. Several scenarios in the ICU make the self-reporting of pain challenging for clinicians (e.g., mechanical ventilation, presence of sedation and/or delirium). SCCM guidelines currently recommends two validated behavioral pain scales to be done in a repetitive and routine manner: the Behavioral Pain Scale (BPS) (Table 1) and the Critical-Care Pain Observation Tool (CPOT) (Table 2).
      a. Assessment scales should be used routinely in all ICU patients. Most nursing protocols assess pain every 4–6 hours while the patient is awake. In addition, it is important to reassess the degree of pain within about 30 minutes to 1 hour after administering an "as-needed" pain medication to determine the appropriateness of the pain medication or dose.
      b. Pain scores should be documented in the medical chart and then used to help formulate daily titrations in pain medications.
      c. Patients should be treated within 30 minutes of a "significant pain" score. A BPS greater than 5 or a CPOT score of 3 or greater, or a numeric rating scale score of 4 or greater is indicative of pain.
   2. The use of vital signs alone is not recommended for assessing pain in the ICU patient. Abnormal vital signs such as tachycardia and hypertension are appropriate for use as a prompt to further investigate the need for pain control.
   3. Further research is needed to determine the effectiveness of a preprocedural pain assessment tool and the ways in which this assessment will affect analgesic administration. A study by Puntillo et al. in 2014 found the procedures most likely to double the patient's pain intensity score (from preprocedure to during-procedure scoring) were chest tube removal, wound drain removal, and arterial line insertion. This study found that higher-intensity pain and pain distress before the procedure were associated with a high risk of increased pain during the procedure (Am J Respir Crit Care Med 2014;189:39-47).

4. Kanji et al. found that the CPOT is a valid pain assessment in noncomatose, delirious adult ICU patients who are not able to reliably self-report the absence or presence of pain (Crit Care Med 2016;44:943-7).

Table 1. Behavioral Pain Scale (BPS)[a]

Item	Description	Score
Facial expression	Relaxed	1
	Partly tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4
Total, range		3–12

[a] A BPS score > 5 indicates significant pain.

Adapted with permission from: Lippincott Williams & Wilkins/Wolters Kluwer Health. Payen J, Bru O, Bosson J, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

Table 2. Critical-Care Pain Observation Tool (CPOT)[a]

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
	All of the above facial movements plus eyelids tightly closed	Grimacing	2
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movement	0
	Slow, cautious movements; touching or rubbing the pain site; seeking attention through movements	Protection	1
	Pulling tube, trying to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension Evaluation by passive flexion and extension of upper extremities	No resistance to passive movements	Relaxed	0
	Resistance to passive movements	Tense, rigid	1
	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2

Table 2. Critical-Care Pain Observation Tool (CPOT)[a] *(continued)*

Indicator	Description	Score	
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: Blocking ventilation, alarms often activated	Fighting ventilator	2
OR Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			0–8

[a] A CPOT score ≥ 3 indicates presence of pain.

Adapted with permission from: Lippincott Williams and Wilkins/Wolters Kluwer Health. Gelinas C, Fillion L, Puntillo K, et al. Validation of the Critical-Care Pain Observation Tool in adult patients. Am J Crit Care 2006;15:420-7.

E. Prevention and Treatment of Pain in the ICU

1. In a patient whose pain is inadequately controlled in the ICU, intravenous opioids are considered first-line treatment for nonneuropathic pain. The PADIS guidelines suggest acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill patients.
2. Preprocedural pain management should be considered in all ICU patients. One study reported that up to 60% of patients did not receive preprocedural systemic pain medication for common procedures and wound care in the ICU, although 89% of patients received a topical anesthetic for central venous catheter placement (Am J Crit Care 2002;11:415-29).
   a. The PADIS guidelines suggest using an opioid at the lowest effective dose for procedural pain management in critically ill patients undergoing a procedure. The American Society for Pain Management Nursing (ASPMN) published recommendations for preprocedural pain management in 2011. The ASPMN recognizes both the psychological and the physical elements of procedural pain and agrees with combining nonpharmacologic and pharmacologic methods. Examples of nonpharmacologic options recommended by ASPMN include relaxation and breathing techniques, imagery, massage, music, thermal measures, and positioning (Pain Manag Nurs 2011;12:95-111). The PADIS guidelines recommend not using inhaled volatile anesthetics for procedural pain management in critically ill adults. The PADIS guidelines also suggest using a nonsteroidal anti-inflammatory drug (NSAID) administered intravenously, orally, or rectally as an alternative to opioids for pain management during discrete and infrequent procedures in critically ill adults. Use of an NSAID topical gel for procedural pain management in critically ill adults is not recommended by the PADIS guidelines.
   b. Preemptive analgesia for chest tube removal is recommended together with nonpharmacologic relaxation techniques. The PADIS guidelines suggest neither local analgesia nor nitrous oxide for pain management during chest tube removal in critically ill patients.
3. Postoperative thoracic epidural anesthesia/analgesia is recommended for patients undergoing abdominal aortic aneurysm treatment. Thoracic epidural anesthesia is “suggested” for traumatic rib fractures in the ICU.

4. Nonpharmacologic therapy for pain
   a. The PADIS guidelines suggest offering cold therapy for procedural pain management in critically ill adults.
   b. The PADIS guidelines suggest offering relaxation techniques for procedural pain management in critically ill adults. Music therapy is suggested for both nonprocedural and procedural pain in critically ill adults.
5. Pharmacotherapy for pain
   a. Intravenous opioids on an as-needed, scheduled, or continuous infusion basis are recommended to treat pain in the ICU. The pharmacokinetics of different opioids may vary; thus, opioids should be chosen according to patient comorbidities and individual needs (Table 3). Fentanyl is the most commonly used intravenous opioids in U.S. adult ICUs.

Table 3. Opiates Commonly Used in the ICU

Drug	Metabolic/Drug Interaction Considerations	Usual CI Starting Dose[a]	Drug-Specific Adverse Effects[b]	Drug Accumulation Factors
Fentanyl	3A4 major substrate	12.5–25 mcg/hr; 0.35–0.5 mcg/kg loading dose follwed by 12.5–25 mcg/hr	Muscle rigidity	Hepatic failure; high volume of distribution; high lipophilicity; unpredictable clearance (long context-sensitive half-time) with prolonged infusion
Morphine	Glucuronidation	1–2 mg/hr	Hypotension, bradycardia from histamine release	Hepatic failure; active metabolite (3- and 6-morphine glucuronide) accumulates in renal failure
Hydromorphone	Glucuronidation	0.25–0.5 mg/hr	Overdose effects from dosing errors (high-potency opiate)	Hepatic failure
Methadone	3A4 and 2B6 major substrates	N/A	QTc prolongation, serotonin syndrome	Long half-life; hepatic and renal failure will delay clearance
Remifentanil	Blood and tissue esterases	Loading dose: 1.5 mcg/kg CI: 0.5–15 mcg/kg/hr	Chest wall rigidity; rebound pain on discontinuation	

[a] Usual starting dose in the ICU for pain management in an opiate-naive patient.

[b] Other common significant adverse effects for all opiates to be considered: Constipation, respiratory depression, bradycardia, hypotension, altered mental status.

CI = continuous infusion.

i. General mechanism of action of opiates: Bind to mu-opioid receptors in the central nervous system (CNS)
ii. Commonly used intravenous opioids in the ICU: Fentanyl, morphine, hydromorphone, remifentanil, and methadone
iii. Tolerance: May quickly develop to all opiates, particularly when given as a continuous infusion. If switching to a different intravenous or oral opiate, equianalgesic dosing may be difficult to estimate, and low starting doses should be considered.

- iv. Significant adverse effects: Decreased respiratory drive: This may be a desired effect in some ICU scenarios; however, a depressed respiratory drive is a critical negative implication during the ventilator weaning process; decreased blood pressure and heart rate, constipation, gastrointestinal (GI) intolerance, altered sensorium.
- v. GI intolerance and constipation: A bowel regimen should be initiated on day 1 unless contraindicated, with assessment for efficacy every 24–48 hours. GI intolerance in the ICU can result in increased time on mechanical ventilation, delayed time to attaining nutritional goals, and prolonged ICU stay. Constipation may also contribute to agitation.
- vi. Altered mental status: Opiates may induce a sedative effect as well as an altered sensorium in some patients. Unless contraindicated, clinicians should consider tapering the opiate dose in an altered patient who has adequate pain control.
- vii. Patient-controlled analgesia: In alert and clinically stable patients, use of patient-controlled analgesia may be considered to titrate to the patient's perceived level of pain. Patient-controlled analgesia may also be useful on discontinuation of continuous infusion opiates.

b. Fentanyl
  - i. Pharmacokinetics: Hepatic metabolism, cytochrome P450 (CYP) 3A4 substrate. Quick onset and short duration of action; lacks a pharmacologically active metabolite. Highly lipophilic, high volume of distribution and protein binding; maintains a three-compartment model; continuous infusion dosing may lead to prolonged and unpredictable clearance (prolonged context-sensitive half-time).
  - ii. Many dosage forms: Injectable (intravenous, intramuscular, intrathecal, epidural), transdermal, transmucosal, nasal spray. Different dosage forms should not be converted on a 1:1 mcg basis; use specific manufacturer recommendations if converting. Injectable form of fentanyl is most commonly used in the ICU setting. The fentanyl patch is not generally appropriate for use in the ICU because of its latent onset (about 12 hours) and erratic/increased absorption in a febrile patient.
  - iii. Adverse effects: Respiratory depression, bradycardia, hypotension, CNS depression, constipation, ileus, risk of serotonin syndrome when used with other serotonergic agents

c. Morphine
  - i. Pharmacokinetics: Hepatic metabolism by glucuronidation to two major active metabolites, morphine-3-glucuronide (45%–55%) and morphine-6-glucuronide (10%–15%). The glucuronide metabolites of morphine are both renally eliminated; accumulation can occur with the chronic use of morphine or in patients with decreased renal function. Morphine-3-glucuronide does not have analgesic activity, but adverse effects may include seizure activity or agitation. Morphine-6-glucuronide does have analgesic activity by the mu-receptor and may cause additive sedation and respiratory depression if accumulation occurs. Continuous morphine infusions are rarely used for analgesia in the ICU setting because of the concerns with the active metabolites.
  - ii. Dosage forms: Injectable (intravenous, subcutaneous, intrathecal, epidural) and oral. Intravenous-to-oral conversion is not a 1:1 mg ratio.
  - iii. Adverse effects: Histamine release may cause significant hypotension; bradycardia, respiratory depression, CNS depression, constipation, ileus.

d. Hydromorphone
  - i. Pharmacokinetics: Hepatic metabolism by glucuronidation to an inactive but potentially neurotoxic metabolite. Low volume of distribution, highly water soluble, and relatively low protein binding.

        ii. Dosage forms: Injectable (intravenous, subcutaneous) and oral; intravenous-to-oral conversion is not a 1:1 mg ratio.
        iii. Adverse effects: CNS alterations (e.g., abnormal dreams, aggressive behavior, altered thinking), respiratory depression, hypotension, constipation
    e. Remifentanil (Ultiva)
        i. Pharmacokinetics: Clearance by blood and tissue esterase; clearance not dependent on organ function. Fast onset and short duration of action with little to no accumulation. High volume of distribution, high protein binding.
        ii. Research primarily done in Europe; limited reported use in U.S. adult ICUs for ongoing analgesic use.
        iii. Dosage form: Injectable only
        iv. Adverse effects: Respiratory depression, hypotension, bradycardia, constipation
        v. Rebound pain: Quick offset (5–10 minutes) may lead to rebound pain and withdrawal symptoms, and additional pain medication may be needed if remifentanil is interrupted or discontinued.
        vi. Benefit in adult ICUs: Decreased time on mechanical ventilation with short-term use (72 hours or less)
    f. Methadone
        i. Pharmacokinetics: Phase I hepatic metabolism to inactive metabolites. Many drug interactions: major substrate of CYP 2B6 and 3A4. Moderate inhibitor of CYP2D6, weak inhibitor of CYP3A4. Longer-acting opiate with variable duration of action (12–48 hours); may accumulate quickly in patients with hepatic failure or patients receiving hemodialysis. Animal studies have found that the d-isomer of methadone works as both a partial mu-agonist and an N-methyl-d-aspartate receptor antagonist (the l-isomer is a full mu-agonist). These properties of the d-isomer are thought to decrease the tolerance effect to other opioids. Methadone is currently marketed as the racemic mixture. On initiating oral methadone, steady state and peak analgesic effect may not be reached for 3–5 days; oversedation and respiratory depression may occur if titrated too quickly.
        ii. Dosage forms: Injectable (intravenous, intramuscular, subcutaneous) and oral. Intravenous-to-oral conversion is not a 1:1.3 mg ratio.
        iii. Adverse effects: Dose-dependent QTc prolongation, altered mental status, respiratory depression, confusion, dizziness, arrhythmias, constipation, risk of serotonin syndrome when used with other serotonergic agents

6. Non-opioid adjunctive pain medications should be considered in combination with opioids to reduce opioid requirements. Clinically stable patients may tolerate a conversion from opiates to non-opiate medications.
    a. Local and regional anesthetics such as bupivacaine. The PADIS guidelines do not recommend the use of intravenous lidocaine as an adjunct to opioid therapy for pain management in critically ill adults.
    b. Acetaminophen (Tylenol, Ofirmev): The PADIS guidelines suggest using acetaminophen as an adjunct to opioids to decrease pain intensity and opioid consumption.
        i. Total daily acetaminophen doses should be considered from all acetaminophen combination products, with a maximum total daily dose of 4 g. Decreased total daily dosing should be considered in patients with significant liver disease or those older than 60 years of age.
        ii. Intravenous acetaminophen: Dose reduction recommended if the creatinine clearance (CrCl) is 30 mL/minute/1.73 m^2 or less or with continuous renal replacement therapy (every 8 hours); contraindicated in severe hepatic disease. The cost of the intravenous formulation of acetaminophen is considerably higher than that of the oral or rectal formulations. The intravenous formulation can also cause hypotension.

   c. Intravenous or oral NSAIDs: Ibuprofen, ketorolac. The PADIS guidelines suggest not routinely using a COX-1 selective NSAID as an adjunct to opioid therapy for pain management in critically ill adults. Use with caution in critically ill patients with renal or hepatic dysfunction. May increase the risk of acute renal failure, bleeding, or GI adverse effects.
   d. Ketamine (Ketalar) has been used for analgesia and sedation in the ICU, primarily in the pediatric population. The PADIS guidelines suggest using low-dose ketamine (1–2 mcg/kg/minute) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU. Published data for the use of ketamine in adults for analgesia and/or sedation is limited, and long-term cognitive effects of ketamine are not known. Data from animal studies suggest a significant decline in cognitive function after continued use of ketamine.
      i. Called a "dissociative anesthetic," providing analgesic activity at subanesthetic doses. It is a schedule III controlled substance and works primarily as an N-methyl-d-aspartate receptor antagonist. Ketamine is void of the constipation, respiratory depression, and hypotensive effects that plague the opiate class.
      ii. May decrease dose requirements of concurrently administered opioids
      iii. Other uses include rapid sequence intubation, refractory pain syndromes, cancer pain, neuropathic pain, asthma (bronchodilatory effects), refractory seizure activity, and depression.
      iv. Dosing range is varied; usual starting dose for analgesia or sedation is 0.1 mg/kg/hour. Reviews of ketamine use in adult ICUs report a dosing range of 0.1–2.5 mg/kg/hour and a range in duration of 3 hours to 9 days.
      v. Significant adverse effects: Mild to severe emergence reactions (e.g., confusion, excitement, irrational behavior, hallucinations, delirium) in around 12% of patients, enhanced skeletal muscle tone, tachycardia, hypertension, hypotension
   e. The PADIS guidelines suggest not offering cybertherapy or hypnosis for pain management in critically ill adults.
   f. The PADIS guidelines suggest offering massage for pain management in critically ill adults.
   g. The PADIS guidelines suggest offering music therapy to relieve both non-procedural and procedural pain in critically ill adults.

7. The PADIS guidelines suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, pregabalin) with opioids for neuropathic pain management in critically ill patients. The PADIS guidelines recommend using neuropathic pain medications with opioids for pain management in ICU adults after cardiovascular surgery. There is a potential for significant adverse effects and drug interactions, requiring close monitoring and follow-up. If the patient is discharged home on an anticonvulsant for neuropathic pain, follow-up should be documented and the primary care provider notified.
   a. Gabapentin (Neurontin)
      i. Suggested starting dose range: 300–600 mg/day divided two or three times daily; requires renal adjustment. The target dose is 900–3600 mg/day in three divided doses.
      ii. Pharmacokinetics: Renally excreted, dose adjusted for reduced CrCl
      iii. Adverse effects: May be severe, including CNS depression, delirium, paresthesias, and asthenias
   b. Carbamazepine (Tegretol)
      i. Suggested starting dose range: 50–100 mg twice daily; use with caution in patients with hepatic impairment, and adjust for a CrCl less than 10 mL/minute/1.73 m^2 or with hemodialysis. The target dose is 100–200 mg every 4–6 hours; the maximum dose is 1200 mg/day.
      ii. Pharmacokinetics: Strong inducer of many CYP enzymes, substrate of CYP3A4. Closely monitor for drug interactions.
      iii. Adverse effects: Somnolence, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), pancytopenia, syndrome of inappropriate antidiuretic hormone

c. Pregabalin (Lyrica)
   i. 50 mg three times daily; may be increased in 1 week depending on tolerability and effect; maximum dose: 100 mg three times daily.
   ii. Pharmacokinetics: 90% excretion in urine
   iii. Adverse effects: Peripheral edema, dizziness, drowsiness, headache, fatigue, weight gain, xerostomia, visual field loss, and blurred vision

F. Analgosedation Method in the ICU: This method of sedation advocates the use of opiate medications before prescribing an anxiolytic/hypnotic medication to provide patient comfort in the ICU unless anxiolytics are otherwise indicated. The PADIS guidelines recommend analgosedation (analgesia is used before a sedative to reach the sedative goal) or analgesia-based sedation (an opioid is used instead of a sedative to reach the sedative goal). Providing pain relief early in the ICU stay may decrease the agitation associated with pain and/or general discomfort while minimizing the use of alternative medications commonly used for agitation (e.g., benzodiazepines). The guidelines recognize that current data using analgosedation are primarily limited to open-label trials, using remifentanil as the analgesic, and mostly conducted in Europe, where critical care staffing and management practices differ from those in the United States. Despite these limitations, it remains notable that studies using the analgosedation method found a significant decrease in benzodiazepine dosage requirements when opiates were the primary medications used for discomfort and agitation. This is a positive step in decreasing the untoward adverse effects of the benzodiazepine class of sedatives. There is a potential for high cumulative doses of opiates with the analgosedation method, necessitating daily monitoring of their adverse effects (e.g., respiratory depression, altered mental status, GI slowing). Opioid use in the ICU also increases the daily risk of delirium development in a dose dependent manner.

G. Data: NONSEDA is a randomized, clinical parallel-group, multinational superiority study comparing no sedation (bolus doses of morphine) and light sedation (propofol for 48 hours then midazolam titrated to a RASS of −2 to −3). There was no difference in 90-day mortality between groups (no sedation 148 [42.4%] vs. light sedation 130 [37%]; 95% CI −2.2 to 12.2; p=0.65). However, 27% of the no-sedation group crossed over to receive sedation during the first 24 hours after randomization.

Patient Case

Questions 1 and 2 pertain to the following case.
T.O. is a 70-year-old man just admitted to the ICU with multiple fractures after a motor vehicle accident. His medical history includes hypertension. He is now agitated after intubation. His laboratory values are normal, and his vital signs include blood pressure 175/95 mm Hg and heart rate 110 beats/minute.

1. Which grouping of initial sedatives is most appropriate at this time?
   A. Fentanyl infusion and midazolam infusion
   B. Propofol infusion and fentanyl as needed
   C. Midazolam as needed and fentanyl as needed
   D. Fentanyl infusion and propofol infusion, if needed

2. After 2 weeks in the ICU, T.O. is being prepared for chest tube removal. He is currently receiving a fentanyl drip with adequate pain control. Which is the best pain management regimen for chest tube removal?
   A. Give intravenous acetaminophen 15 minutes before chest tube removal.
   B. Make no change in pain treatment because his current pain regimen is adequate.
   C. Increase his pain medication infusion dose by 50% the morning of his chest tube removal.
   D. Give fentanyl 50 mcg injectable 15 minutes before chest tube removal.

III. AGITATION IN THE INTENSIVE CARE UNIT

A. Agitation in the ICU – Maintaining patient comfort for the duration of an ICU stay can be extremely challenging, requiring significant resources and daily discipline from the nursing, medical, and pharmacy team. Ongoing research has improved our understanding of the consequences of either under- or overtreating agitation in the ICU, and clinicians should continue to apply this knowledge to their daily selection and titration of medications. Treatment of a patient who presents with agitation must always begin with attempts to identify and correct the etiology of the agitation. Common causes of agitation in the ICU include pain, delirium, hypoxia, hypoglycemia, dehydration, and drug or alcohol withdrawal. Close inspection of significant patient variables will also help determine the appropriate sedative:
   1. Pain control
   2. Substance abuse and smoking history
   3. Neurologic function: Baseline and acute mental status, history of seizure activity, dementia, psychiatric history
   4. Clinical variables: Blood pressure, heart rate, respiratory rate
   5. Comorbidities (baseline and acute): Cardiac, renal, hepatic, gastric, pulmonary, pancreatic
   6. Home medication use: Any medication from which a patient could withdraw: Benzodiazepines, opioids, nicotine, antidepressants, other γ-aminobutyric acid (GABA) receptor agonists

B. Common Medications for the Treatment of Agitation – Include propofol, dexmedetomidine, and benzodiazepines (usually lorazepam and midazolam) (Table 4). Benzodiazepines are first-line agents for status epilepticus, alcohol withdrawal, benzodiazepine dependence or withdrawal, and are useful for deep sedation or amnesia and with the use of neuromuscular blockade. Other indications for benzodiazepines may exist, which must be scrutinized throughout the ICU stay.

Table 4. Sedatives for Patients on Mechanical Ventilation in the ICU

Drug	Onset and Duration	Precautions for Use	CYP Substrate (major)	Usual Dose	Significant Adverse Effects
Propofol	Onset: 1 min Duration: shortterm: 0.5–1 hr; long term > 7 days: variable; 25–50 hr has been observed (depends on depth and time on sedation)	Hypotension, bradycardia, hepatic/ renal failure, pancreatitis	2B6	5–50 mcg/kg/min; 0.3–3 mg/kg/hr	Hypotension, pancreatitis, respiratory depression, bradycardia, PRIS
Dexmedetomidine	Onset: 5–10 min (with LD) 1–2 hr (without LD) Duration: 1–2 hr	Hepatic failure; symptomatic bradycardia	2A6	LD: 0.5–1 mcg/kg (optional) MD: 0.2–0.7 mcg/kg/hr	Hypo/hyper-tension, bradycardia, pyrexia
Lorazepam	Onset: 5–20 min Duration: 4–8 hr; prolonged with continuous infusion	Delirium, renal failure	N/A	Intermittent: 1–4 mg IV every 4–6 hr	Oversedation, propylene glycol toxicity
Midazolam	Onset: 3–5 min Duration: 2–6 hr, prolonged with continuous infusion	Hepatic failure, end-stage renal failure or dialysis, delirium	3A4 (active metabolite)	0.02–0.1 mg/kg/hr	Oversedation

CI = continuous infusion; IV = intravenously; LD = loading dose; MD = maintenance dose; N/A = not applicable; PRIS = propofol-related infusion syndrome.

C. SCCM provides the following statement in the PADIS guidelines regarding sedation in the ICU: “We suggest using either propofol or dexmedetomidine over benzodiazepines [midazolam or lorazepam] for sedation in critically ill, mechanically ventilated adults” and those after cardiac surgery. SCCM states that “benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients.” Two randomized studies evaluated the differences in clinical outcomes while adult ICU patients were receiving sedation with either a benzodiazepine or a non-benzodiazepine strategy. Heterogeneity occurred among the findings of these two studies (see No. 1 and No. 2 below), which may be partly because of differences in study design.

1. The MENDS study compared the sedative effects of lorazepam and dexmedetomidine in medical and surgical adult ICU patients (n=103). Dexmedetomidine had more “delirium-free + coma-free” days than lorazepam (7 vs. 3 days, p=0.01), and the prevalence of “delirium or coma” was lower in the dexmedetomidine group (87% vs. 98%, p=0.03). The assessment of “delirium-free + coma-free” was a more appropriate outcome to evaluate than “delirium without coma,” given that delirium cannot be assessed in patients with coma. More patients were within 1 point of their RASS goal with dexmedetomidine (67%) than with lorazepam (55%), p=0.008, but there was no difference in mechanical ventilator–free days, ICU length of stay, or 28-day mortality. This study has been criticized because both groups received continuous infusions of sedatives without additional bolusing, whereas in clinical practice, most practitioners would bolus lorazepam before increasing the infusion rate. In addition, patients were not required to have a spontaneous awakening trial (SAT). (JAMA 2007;298:2644-53).

2. The SEDCOM study compared the sedative effects of midazolam with those of dexmedetomidine in medical and surgical adult ICU patients (n=366). The prevalence of delirium was lower in the dexmedetomidine group (54%) than in the midazolam group (76.6%), $p<0.001$. Median time to extubation was shorter in the dexmedetomidine group (3.7 days) than in the midazolam group (5.6 days), $p<0.01$; however, the times in target sedation range, ICU length of stay, and mortality were no different between the two groups. This study did allow bolus dosing of study drugs, and patients were required to have an SAT if safety criteria were met (JAMA 2009;301:489-99).

D. Clinical Outcome Differences Among Sedative Agents in Medical and Surgical ICU Patients: A meta-analysis, “Benzodiazepine versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated Critically Ill Adults,” reviewed trials from 1996 to 2013 (Crit Care Med 2013;41:S30-8):
   1. Studies from this review contained the following criteria: (1) randomized controlled parallel-group design; (2) medical and surgical adult ICU patients on mechanical ventilation receiving intravenous sedation; (3) patients receiving a non-benzodiazepine (propofol 1% or dexmedetomidine) compared with a benzodiazepine (lorazepam or midazolam); and (4) patients having predefined outcomes. Excluded cardiac surgery and obstetric patients.
   2. Four primary outcomes from six randomized trials were reported in the review (1235 patients):
      a. ICU length of stay (all six studies reported): ICU length of stay was longer in a benzodiazepine strategy than in a non–benzodiazepine-based strategy (mean difference 1.6 days; 95% confidence interval [CI], 0.72–2.5; p=0.0005).
      b. Duration of mechanical ventilation (four studies reported): Longer duration of mechanical ventilation in a benzodiazepine-based strategy than in a non–benzodiazepine-based strategy (mean difference 1.9 days; 95% CI, 1.7–2.09; p=0.00001)
      c. Delirium prevalence (two studies reported): No difference in delirium prevalence between a benzodiazepine and a non–benzodiazepine-based strategy (relative risk [RR] 0.98; 95% CI, 0.76–1.27; p=0.94)
      d. Short-term (45 days or less) all-cause mortality (four studies reported): No difference in risk of death between a benzodiazepine and a non–benzodiazepine-based strategy (RR 0.98; 95% CI, 0.76–1.27, p=0.94)

E. Propofol
   1. SCCM suggests using a non-benzodiazepine (propofol or dexmedetomidine) for sedation to improve clinical outcomes in mechanically ventilated patients. Throughout the past decade, propofol has been increasingly used worldwide for sedation in the ICU. Propofol’s short duration of action, lack of accumulation, and relatively clean adverse effect profile at low to moderate doses makes it an appealing alternative.
   2. Mechanism of action: General anesthetic by potentiation of the $GABA_A$ receptor; may inhibit *N*-methyl-D-aspartate receptor activity at high doses. Propofol decreases cardiac β-adrenergic responsiveness and attenuates β-adrenergic signal transduction in cardiac myocytes, resulting in direct cardiac depressive effects.
   3. Pharmacokinetics: Hepatic conjugation; clearance may be prolonged (from minutes to hours) in patients with severe hepatic impairment or cirrhosis or with long-term infusions as it redistributes from fat and muscle to plasma. Highly lipophilic pharmacokinetics and a large volume of distribution lead to extensive tissue distribution. Propofol maintains a three-compartment linear model: plasma, rapidly equilibrating tissues (e.g., major organs), and slowly equilibrating tissues (e.g., fat deposits). Substrate of CYP 2B6, 2C9, 2C19, and 3A4; pharmacokinetic studies of healthy volunteers show a 25% increase in propofol plasma concentrations when given with midazolam, a weak CYP 3A4 and 2C9 inhibitor.

4. Lipid formulation considerations: Standard propofol is a 1% (10 mg/mL) lipid emulsion containing 1.1 kcal/mL (0.1 g of fat per 1 mL of propofol); this should be accounted for when calculating nutritional intake (e.g., propofol at 50 mcg/kg/minute in a 70-kg patient would provide around 500 calories per day contributed by fat). Propofol contains 0.005% disodium edetate (EDTA) to decrease the rate of microorganism growth, which is known to chelate trace metals, including zinc. Zinc supplementation should be considered in patients at high risk of zinc deficiency (sepsis, burns, large-volume diarrhea) if propofol is used for more than 5 days. Strict aseptic technique must be followed when handling propofol; manufacturers recommend discarding propofol bottles and changing intravenous tubing every 12 hours to decrease the risk of contamination. Propofol is not contraindicated in patients with egg or soybean allergies as historically thought. Propofol contains egg yolks, and most patients are allergic to egg whites. Propofol contains soybean oil not soybean-derived proteins, which have been linked to allergic reactions.
5. Dosing range for ICU sedation: Usual starting dose 5–10 mcg/kg/minute, titrated every 5–10 minutes to goal sedative effect. Abrupt discontinuation of propofol is not recommended because of its rapid clearance (5–10 minutes).
6. Data: In a multicenter European trial (PRODEX), Jakob et al. compared propofol (n=249) with dexmedetomidine (n=251) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and spontaneous breathing trials (SBTs), and pain was treated with fentanyl boluses. Proportion of time in target RASS (0, −3) without rescue therapy was the same in the propofol group (65%) as in the dexmedetomidine group (65%). There was no difference in median time on mechanical ventilation in propofol (5 days) versus dexmedetomidine (4 days), p=0.24. Patients' ability to communicate discomfort was better in the dexmedetomidine group. Rates of hypotension and bradycardia were similar between the two groups. Critical illness polyneuropathy was more common in the propofol group (n=11) than in the dexmedetomidine group (n=2), p<0.02. The composite outcome of agitation, anxiety, and delirium occurred in propofol (29%) versus dexmedetomidine (18%) (p=0.008) (JAMA 2012;307:1151-60).
7. Adverse effects: Bradycardia and hypotension (may be more common or severe in patients with cardiac dysfunction, intravascular volume depletion, or low systemic vascular resistance); respiratory depression, hypertriglyceridemia (most institutions use a threshold of 800–1000 as a cutoff of when to stop propofol), pancreatitis with or without hypertriglyceridemia, PRIS
8. PRIS: This is a rare but life-threatening complication of propofol, usually occurring at doses greater than 50 mcg/kg/minute for 48 hours or more. The mechanism of PRIS may include alterations in hepatic metabolism of the lipid emulsion, leading to an accumulation of ketone bodies and lactate and/or disruptions in the mitochondrial respiratory chain and inhibition of oxidative phosphorylation. Patients with urea cycle disorders may experience alterations in propofol metabolism within 24–48 hours of propofol use. Consider avoiding in patients with acute liver failure, or pancreatitis, because the symptoms of PRIS may be difficult to distinguish from the underlying disease state abnormalities. PRIS carries a high mortality rate, and propofol should be discontinued immediately if symptoms are present.
    a. Clinical characteristics of PRIS: Metabolic acidosis, acute renal failure, cardiovascular collapse, cardiac arrhythmias including Brugada-like syndrome, rhabdomyolysis, myoglobinemia, myoglobinuria, hyperkalemia, hypertriglyceridemia, elevated creatine kinase concentrations
    b. Risk factors for PRIS or other adverse effects of propofol: Neurologic injury, sepsis, use of vasoactive medications, high-dose propofol, acute liver failure

F. Dexmedetomidine
1. SCCM suggests that in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, dexmedetomidine infusions rather than benzodiazepine infusions should be administered for sedation to reduce the duration of delirium.

2. Mechanism of action: Highly selective and dose-dependent α_2-adrenoceptor agonist in the CNS. Dexmedetomidine provides a hypnotic and sedative effect by inhibition of norepinephrine release from the locus coeruleus; dexmedetomidine also produces a weak antinociceptive effect by way of inhibition of neuronal transmission through presynaptic C-fibers and release of substance P, and hyperpolarization of postsynaptic α receptors in the dorsal horn of the spinal column. Dexmedetomidine does not directly affect respiratory drive; therefore, intubation is not required with use. Dexmedetomidine is considered a weak sedative and would not be appropriate for use when deep sedation is required (e.g., in a patient requiring neuromuscular blockade). Both anterograde amnesia and retrograde amnesia have been described in some patients (20%–50%) in adult and pediatric studies. A benzodiazepine may be required if full amnesia is desired because of the clinical scenario.
3. Pharmacokinetics: Hepatic by glucuronidation and renal excretion. Onset with loading dose 15–20 minutes; onset without loading dose greater than 20 minutes to 1 hour; terminal half-life = 3 hours (may be significantly prolonged in hepatic impairment). Highly protein bound 94%.
4. Clinical effects: Sedation and weak opiate-sparing antinociceptive effects.
5. Dosing for ICU sedation: Optional loading dose 0.5–1 mcg/kg intravenously for 10 minutes, followed by 0.2–0.7 mcg/kg/hour. The loading dose may initially cause severe tachycardia and hypertension, but it can then quickly lead to significant bradycardia and/or hypotension secondary to receptor saturation. Because of these untoward hemodynamic effects, the loading dose is rarely administered in clinical ICU practice on initiation of dexmedetomidine, and the drip is usually initiated at 0.2–0.4 mcg/kg/hour. For the maintenance infusion dose, randomized trials have safely used dexmedetomidine at higher than manufacturer-recommended doses, up to 1.5 mcg/kg/hour. Clinical efficacy with doses greater than 1.5 mcg/kg/hour remains unclear. Other routes of administration have been described for dexmedetomidine, including intramuscular, subcutaneous, epidural, and intranasal.
6. Duration of use: Although the package insert recommends a therapy of 24 hours or less, randomized trials have used dexmedetomidine for up to 5–7 days; thus, ICU clinicians often administer dexmedetomidine for longer than 24 hours. Safety beyond 7 days of use has not been well established.
7. Data: The Dexmedetomidine to Lessen ICU Agitation (DahLIA) study was a double-blind placebo-controlled, parallel-group randomized clinical trial in 15 ICUs in Australia and New Zealand in which 39 patients were randomized to dexmedetomidine and 32 patients to placebo. At 7 days, dexmedetomidine increased ventilator-free hours compared with placebo (median, 144.8 hours vs. 127.5 hours, 95% CI 4 to 33.2 hours, p=0.01). Patients in the dexmedetomidine group had decreased time to extubation compared with placebo (median 21.9 hours vs. 44.3 hours, 95% CI 5.3 to 3.1 hours, p<0.001). An accelerated resolution of delirium was found in the dexmedetomidine group compared with placebo (median, 23 hours vs. 40 hours, 95% CI, 3 to 28 hours, p=0.01). However, propofol use was common in both groups after randomization (72% in the dexmedetomidine group vs. 88% in the placebo group) (median cumulative dose 980 mg (IQR 280–3050) vs. 5390 mg (IQR 1880–10,803), p<0.001).
8. Data: The DESIRE trial was a open-label, multicenter randomized clinical trial conducted in eight ICUs in Japan in which 100 patients with sepsis were randomized to dexmedetomidine and 101 patients with sepsis were randomized to placebo. Mortality at 28 days was not different between the two groups (23% in the dexmedetomidine group vs. 31% in the placebo group; HR 0.69; 95% CI, 0.38–1.22; p=0.20). Ventilator-free days over 28 days were not different between groups (median 20 days (IQR 5–24) in the dexmedetomidine group vs. 18 days (IQR 0.5–23) in the control group (p=0.20).

9. Data: SPICE III was an open-label, randomized controlled trial comparing dexmedetomidine as primary sedation with usual care (propofol, midazolam, or other sedation) in patients receiving less than 12 hours of mechanical ventilation who are expected to be on the ventilator for at least one additional day. The target RASS goal was -2 to +1. Death at 90 days occurred in 569 of 1956 (29.1%) of the usual care group and 566 of 1948 (29.1%) of the dexmedetomidine group (adjusted risk difference 0.0 percentage points; 95% CI, –2.9 to 2.8). In the dexmedetomidine group, 64% of patients additionally received propofol, 3% received midazolam, and 7% received both during the first 2 days after randomization. Sixty percent of patients received propofol, 12% received midazolam, and 20% received both in the usual care group. Given the many sedatives administered in both groups, application of the study results is difficult. In the dexmedetomidine group, bradycardia and hypotension occurred in 5.1% and 2.7% of patients. A post hoc analysis of SPICE III included 703 mechanically ventilated patients. Over the first 5 ICU days, more patients in the dexmedetomidine group had a temperature of 38.3°C or greater (43.3% vs 32.7%, p=0.004) and 39.0°C or greater (19.4% vs 12.5%, p=0.013). A post hoc subgroup analysis of SPICE III compared the effect of dexmedetomidine versus usual care on vasopressor requirements in patients with septic shock. This subroup included 83 patients, of which, 44 (53%) received dexmedetomidine and 39 (47%) usual care. In the first 48 hours, median NEq dose was 0.03 [0.01, 0.07] μg/kg/min in the dexmedetomidine group and 0.04 [0.01, 0.16] μg/kg/min in the usual care group (p = 0.17). Patients in the dexmedetomidine group had a lower NEq/MAP ratio, meaning lower vasopressor requirements to maintain the target MAP.
10. Data: MENDS 2 is multicenter, double-blind trial comparing dexmedetomidine to propofol. No difference was found between dexmedetomdine and propofol in the number of days alive and without delirium of coma (adjusted median 10.7 vs 10.8 days; odds ratio, 0.96; 95% CI 0.74–1.26), ventilator free days (adjusted median, 23.07 vs. 24 days, odds ratio 0.98; 95% CI, 0.63–1.51), or death at 90 days 38% vs. 39%; hazard ratio, 1.06; 95% CI 0.74–1.52).
11. Data: Dexmedetomidine was compared with other sedatives in critically ill mechanically ventilated adults. A total of 77 randomized trials were included. Compared with other sedatives, dexmedetomidine reduced the risk of delirium (RR 0.67; 95% CI, 0.55–0.81; moderate certainty), duration of mechanical ventilation (mean difference [MD] -1.8 hours; 95% CI, -2.89 to -0.71; low certainty), and ICU length of stay (MD -0.32 days; 95% CI, -0.42 to -0.22; low certainty). The risk of bradycardia (RR 2.39; 95% CI, 1.82–3.13; moderate certainty) and hypotension (RR 1.32; 95% CI, 1.07–1.63; low certainty) was increased with dexmedetomidine.
12. Data: A rapid practice guideline was published looking at use of dexmedetomidine for sedation in mechanically ventilated adult patients in the ICU. It suggested use of dexmedetomidine over other sedative agents if the reduction in delirium was more highly valued than the potential for hypotension and bradycardia.
13. Adverse effects: Tachycardia, pyrexia bradycardia, hypertension, hypotension, dry mouth. Should generally be avoided in patients with acute decompensated heart failure or advanced heart block
14. Other potential uses in the ICU: Procedural sedation, palliative care pain and anxiety control, adjunct to opiates for sickle cell crisis, adjunct to benzodiazepines or propofol for alcohol withdrawal, bridge to extubation while tapering off longer-acting sedatives and/or opiates, to provide sedation and anxiolysis during noninvasive mechanical ventilation

G. Lorazepam (Ativan)

1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic $GABA_A$ receptor, undergoes hepatic clearance by conjugation to inactive compounds; moderate to high volume of distribution and high protein binding. Onset of action is 15–30 minutes, slower than more lipophilic benzodiazepines (e.g., midazolam). Duration of action of intermittent dosing is 4–8 hours. As a continuous infusion, clearance of lorazepam decreases in an unpredictable fashion, and prolonged sedation may occur.

2. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties; however, studies report that patients who received benzodiazepines in the ICU may maintain delusional versus factual memories.
3. Dosing range: 1–4 mg every 4–6 hours intermittent dosing is recommended before using continuous infusion; accumulation and prolonged awakening times with continuous infusion of lorazepam may occur because of prolonged duration of action.
4. Data: Carson et al. studied the number of days on mechanical ventilation in medical ICU patients receiving intermittent lorazepam (n=64) compared with continuous infusion propofol (n=68); each group underwent daily interruption of sedation if the fraction of inspired oxygen (FIO_2) was less than 80%. Median time on mechanical ventilation was 9 days in the lorazepam group versus 4.4 days in the propofol group, p=0.006; ICU length of stay was 12.7 days in the lorazepam group versus 8.6 days in the propofol group (p=0.05); no difference in hospital mortality. Delirium was not assessed in this study (Crit Care Med 2006;34:1326-32).
5. Propylene glycol toxicity: Because of its insolubility, injectable lorazepam is diluted in propylene glycol. Propylene glycol toxicity can occur with lorazepam infusions for more than 48 hours, particularly at doses of 6–8 mg/hour or greater, and can manifest as new-onset renal failure, respiratory failure, metabolic acidosis, and altered mental status. Most hospitals cannot measure quantitative levels of propylene glycol; therefore, surrogate markers of propylene glycol toxicity such as an elevated osmolar gap (greater than 10 mOsm/kg) and elevated anion gap with new metabolic acidosis are recommended for monitoring. If these metabolic abnormalities are present while on a lorazepam infusion, lorazepam should be discontinued.
6. Other adverse effects: Paradoxical agitation, confusion, prolonged duration of sedative action, respiratory depression, hypotension, bradycardia

H. Midazolam (Versed)
   1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic $GABA_A$ receptor; undergoes phase I hepatic metabolism to an active glucuronidated metabolite, α_1-hydroxymidazolam, which is then renally excreted. A short- to medium-acting benzodiazepine in patients with normal renal and hepatic function. CYP3A4 substrate. Midazolam is highly lipophilic, has a large volume of distribution, and is highly protein bound.
   2. Clearance: Clearance of midazolam or its metabolite is significantly altered if either hepatic (primary drug accumulation) or renal (active metabolite α-hydroxymidazolam accumulation) functions are significantly impaired. Continuous renal replacement therapy partly clears the active metabolite but does not effectively clear the parent compound and is therefore not recommended as a method for definitive midazolam clearance (Am J Kidney Dis 2005;45:360-71). High lipophilicity and a large volume of distribution may lead to significant drug accumulation and a depot effect in the ICU patient. In general, clearances of midazolam infusions have wide interpatient variability in the ICU, and emergence times may be significantly prolonged.
   3. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties.
   4. Dosing range: 1–4 mg every 2–4 hours intermittently or as needed should be considered before initiating continuous infusion. Older adult patients may tolerate only 1–2 mg per dose.

5. Data: In a multicenter European trial (MIDEX), Jakob et al. compared midazolam (n=251) with dexmedetomidine (n=249) for sedation in prolonged mechanical ventilation. Patients in both groups were treated with daily sedation interruption trials and SBTs, and pain was treated with fentanyl boluses. There was no difference in the primary outcome: proportion of time in target RASS (0, -3) without rescue therapy in the midazolam group (56%) versus the dexmedetomidine group (60%). Median time on mechanical ventilation was lower in the dexmedetomidine group (5 days) than in the midazolam group (6.8 days), p=0.03. Patients in the dexmedetomidine group were more arousable, more cooperative, and better able to communicate discomfort or pain to clinical staff than were patients in the midazolam group. Hypotension occurred more often in the dexmedetomidine group (20.6%) than in the midazolam group (11.6%; p=0.007); and bradycardia was more common in the dexmedetomidine group (14.2%) than in the midazolam group (5.2%; p<0.001). The two treatment groups showed no difference in neurocognitive adverse events after 48 hours of follow-up, including agitation, anxiety, and delirium (JAMA 2012;307:1151-60).
6. Adverse effects: Paradoxical agitation and prolonged duration of sedative action, respiratory depression, hypotension, bradycardia

I. Titration of Sedation in the ICU

1. Titration of medications using a sedation protocol to a goal level of sedation is arguably one of the most salient clinical practice standards within ICU care. This titration practice has consistently been shown to decrease time on mechanical ventilation, decrease ICU length of stay, and decrease rates of tracheostomy, which may all result in faster physical and cognitive rehabilitation time.
    a. The goal level of sedation should be reassessed daily, documented, and communicated clearly to the nursing and medical staff because the goal may change throughout a patient's ICU stay.
    b. Level of sedation should be assessed every 2–4 hours throughout the day and evening. Consider assessing every 4 hours during nighttime sleeping hours to minimize sleep interruption.
    c. The two validated sedation scales currently recommended by the PADIS guidelines are the RASS (Table 5) and the Riker Sedation-Agitation Scale (Table 6).
2. Recommended methods for titration of medications include either (1) titration to a "light" versus "deep" level of sedation, unless clinically contraindicated, or (2) daily SAT. The PADIS guidelines suggest using light sedation (vs. deep sedation) in critically ill, mechanically ventilated adults. Light sedation is defined as a RASS of –2 to +1 or an SAS of 3 or 4, per the PADIS Guidelines. However, a pilot study from 2022 suggested that a RASS of –1 and an SAS of 4 indicate light sedation.
    a. Patients should receive sedation only if required.
    b. Sedatives should be titrated to allow patient responsiveness and awareness, as shown by patients' ability to purposefully respond to a combination of any three of the following actions on request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes. A numerical score on a sedation scale may not fully represent a patient's ability to follow purposeful commands.
3. Data: In a multicenter, prospective, longitudinal Australian and New Zealand Study, Shehabi et al. evaluated 251 medical/surgical patients who were ventilated and sedated for 24 hours or more. Within 4 hours of initiating ventilation, deep sedation occurred in 191 patients (76.1%) and in 171 patients (68%) at 48 hours. Early deep sedation was an independent predictor of time to extubation (HR 0.90; 95% CI, 0.87–0.94; p<0.001), hospital death (HR 1.11, 95% CI, 1.02–1.20; p=0.01), and 180-day mortality (HR 1.08, 95% CI, 1.01–1.16; p=0.026) (JAMA 2012;307:1151-60).

4. In a single-center, nested cohort study within the Awakening and Breathing Controlled (ABC) randomized trial, Seymour et al. evaluated 140 patients for whom hourly doses of benzodiazepines and propofol during the daytime (7 a.m. to 11 a.m.) and nighttime (11 p.m. to 7 a.m.) for 5 days were measured. Greater daytime benzodiazepine doses were independently associated with failed SBT and extubation and subsequent delirium in adjusted models ($p<0.02$ for all). A failed SBT ($p<0.01$) and delirium ($p=0.05$) were associated with nighttime increases in benzodiazepine doses (Crit Care Med 2012;40:2788-96).

J. SAT Paired with SBT: The daily coordination of an SAT completed before an SBT is a method of weaning sedation before attempts at breathing trials in order to maximize a patient's chances of weaning from mechanical ventilation. This pairing of an SAT before an SBT is becoming recognized as an important component to ICU care and management of sedation. Important safety screens are incorporated into the daily SAT because studies have shown that the SAT is not appropriate for all ICU patients. If a patient does not pass the safety screen and does not undergo the SAT, this should not preclude the appropriate titration of sedatives to a goal level of sedation throughout the remainder of the day:

1. SAT safety screen (criteria may vary; published trial protocols have had variations): If any are present, discontinue the protocol and repeat in 12–24 hours or according to hospital protocol:
    a. Current RASS greater than 2; or goal for deeper sedation (e.g., RASS -3 to -5)
    b. Active seizures requiring a continuous infusion of a sedative to control
    c. Active alcohol withdrawal requiring a continuous infusion of a sedative to control
    d. FIO_2 of 70% or greater (these criteria are not consistently present among published trial protocols)
    e. Neuromuscular blockade
    f. Myocardial ischemia in previous 24 hours or ongoing myocardial ischemia
    g. Intracranial pressure (ICP) greater than 20 mm Hg or need for control of ICP
2. If pass SAT safety screen, begin SAT: Hold continuous sedative and analgesic infusions. Bolus opioids are recommended for breakthrough pain. Continuous opioid infusions allowed to continue while stopping sedatives if presence of active pain. If the patient "passes" the SAT, continue to the SBT safety screen.
3. SAT failure (if any are present, discontinue the protocol, and repeat in 12–24 hours or according to hospital protocol):
    a. Anxiety/agitation/pain present (e.g., RASS greater than +1 for 5 minutes or more)
    b. Respiratory rate greater than 35 breaths/minute for 5 minutes or more
    c. Oxygen saturation less than 88% for 5 minutes or more
    d. ICP greater than 20 mm Hg
    e. Acute cardiac ischemia or arrhythmia
    f. Respiratory or cardiac distress (e.g., heart rate increase of 20 beats/minute or greater, heart rate less than 55 beats/minute, use of accessory muscles, abdominal paradox, diaphoresis, or dyspnea)
4. If SAT fails: Consider giving patient bolus opioids first (up to three doses in 1 hour) before restarting infusion. Reinitiate sedation infusion, if necessary, at half the previous dose and titrate to goal. Determine the reasons for SAT failure. Repeat SAT steps in 12–24 hours or according to hospital protocol.
5. SBT safety screen (if any are present, discontinue the protocol; repeat in 12–24 hours or according to hospital protocol):
    a. Agitation
    b. Oxygen saturation less than 88%, FIO_2 greater than 50%
    c. PEEP (positive end-expiratory pressure) of 7 cm H_2O or greater
    d. Myocardial ischemia in previous 24 hours
    e. Increasing vasopressor requirements
    f. Lack of inspiratory efforts

6. SBT: If a patient tolerates the SBT for 30 to 120 minutes, consider extubation.
7. SBT failure:
    a. Respiratory rate greater than 35 breaths/minute (for more than 5 minutes) or less than 8 breaths/minute
    b. Oxygen saturation less than 88% for more than 5 minutes
    c. ICP greater than 20 mm Hg, mental status change
    d. Acute cardiac ischemia or arrhythmia
    e. Respiratory distress (use of accessory muscles, abdominal paradox, diaphoresis, and dyspnea)
8. If SBT fails: Place the patient on prior ventilator settings. Repeat bundle in 12–24 hours or according to hospital protocol.

K. Sedation Protocol Compared with the Paired SAT-SBT Protocol: Studies comparing a standard sedation protocol with daily pairing of a SAT with SBT have shown decreased days on mechanical ventilation, days in the ICU, and decreased rates of delirium when the SAT is paired with the SBT.
    1. The ABC trial included 336 mechanically ventilated patients from four tertiary care hospitals. Patients were randomized to patient-targeted sedation protocol plus the SBT (“usual care” control group) or to daily SAT paired with the SBT (intervention group). Both groups were deeply sedated on enrollment (RASS -4), and both groups had been admitted for 2.2 days before enrollment. In the intervention group, patients who passed the safety screen underwent an SAT: sedatives and analgesics used for sedation were discontinued, and analgesics used for active pain were continued. Patients “passed” their SAT if they opened their eyes to command or tolerated being off sedation for at least 4 hours without meeting failure criteria. The mean ventilator-free days was 11.6 days in the usual care control group versus 14.7 days in the SAT plus SBT group (p=0.02). The time to discharge was 12.9 days in the control group versus 9.1 days in the intervention group (p=0.01). Self-extubations were higher in the intervention group, but there was no difference in self-extubations requiring reintubation between groups. Rates of delirium assessed by the confusion assessment method for the intensive care unit (CAM-ICU) were no different between groups (74% vs. 71%).
    2. The first study evaluating the ABCDE (Awakening and Breathing Coordination, Delirium Monitoring/Management, and Early Mobility) Bundle compared clinical outcomes in patients before (n=146) and after (n=150) bundle-protocol implementation; 187 patients were on mechanical ventilation. The bundle protocol consisted of a daily-paired SAT/SBT, delirium screening with the CAM-ICU every 8 hours, and an early mobility protocol. The “before” bundle patients were enrolled from February to October 2011; the “after” bundle patients were enrolled from October 2011 to April 2012. There were some differences in patient type on admission, including more elective admissions in the post-bundle group (39 vs. 30), more cardiothoracic surgery patients in the post-bundle group (20 vs. 6), more surgical patients in the pre-bundle group (21 vs. 11), and more patients coming from an outside hospital in the pre-bundle group (9 vs. 1). The post-bundle group had more median ventilator-free days (24 vs. 21 days, p=0.04), less delirium at any time (49 vs. 62%, p=0.03), and shorter percentage of ICU days with delirium (33.3 vs. 50 %, p=0.003) (Crit Care Med 2014;42:1024-36).
    3. The SLEAP investigators from the Canadian Critical Care Trials Group studied the outcomes of patients receiving a daily sedation protocol alone versus patients receiving a daily sedation protocol plus a daily sedation interruption (Crit Care Med 2015;43:557-66; Crit Care Med 2015;43:2180-90; JAMA 2012;308:1985-92). From January 2008 to July 2011, 430 patients were enrolled from 16 tertiary care medical and surgical ICUs. Only opiate and benzodiazepine infusions were allowed in the study. According to the sedation-alone protocol, the RASS goal was -3 to 0, and the Sedation-Agitation Scale (SAS) goal was 3 or 4. Nurses assessed sedation levels on an hourly basis and titrated medications every 15–30 minutes to achieve sedation goals. If patients were oversedated in either group (SAS 1 or 2; RASS −4 or −5), infusions were discontinued. According to the sedation protocol with daily sedation

interruption, nurses stopped benzodiazepine and opiate infusions once a day and assessed hourly for wakefulness (e.g., a light SAS or RASS score, plus ability to follow at least three commands).

a. Clinical outcomes (published 2012): There was no difference in the primary outcome of time to successful extubation between the two groups (7 days in both groups). There was a significant difference in time to extubation in the prespecified surgical/trauma group between sedation protocol with daily sedation interruption and sedation protocol alone (6 vs. 13 days; hazard ratio [HR] 2.55; 95% CI, 1.40–5.44). No difference in time to extubation was detected between groups among medical ICU patients (9 vs. 8 days; HR 0.92; 95% CI, 0.72–1.18). However, significantly lower daily doses of both benzodiazepines and opiates boluses and continuous infusions were used in the sedation protocol–alone group than in the sedation protocol plus interruption group. Although the sedation protocol suggested to target light sedation, the actual mean RASS/SAS was not reported for either group making it unclear how deeply sedated either group was.

b. Delirium outcomes (published 2015): Delirium by the Intensive Care Delirium Screening Checklist (ICDSC) was diagnosed in 53.8% of patients in the study; there was no difference in delirium in the sedation protocol–alone group versus the protocol plus daily sedation interruption group. Patients who had delirium had a longer duration of mechanical ventilation, longer ICU and hospital stay, longer use of restraints, higher rates of tracheostomy, and higher incidence of unintentional device removal. Patients with delirium received almost the twice the mean dose of midazolam equivalents/patient/day (104 mg vs. 57 mg), higher fentanyl equivalents/patient/day (1497 mcg vs. 1150 mcg), more frequent use of anticholinergics (18 vs. 8.6%), and more frequent use of trazadone or zopiclone (17.7 vs. 9.8%) than did patients who were not delirious. Patients who developed delirium had a higher incidence of alcohol and cigarette use than did patients who did not develop delirium.

c. Recall in ICU survivors (published 2015): The SLEAP investigator study did patient interviews on days 3, 28, and 90 post-ICU discharge to determine differences in recall between the sedation-alone protocol group and the protocol plus daily sedation interruption group. There were no differences in type of recall between the sedation strategies. Delusional memories were common at day 28 (70% of patients) but were unrelated to the presence of delirium or the total dose of benzodiazepines or opiates. Patients with no recall had received lower total doses of benzodiazepines than had patients with recall. Emotional memories such as panic and confusion declined over time.

Table 5. Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or has aggressive behavior toward staff
+2	Agitated	Frequently nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert but has sustained (> 10 s) awakening, with eye contact, to voice
−2	Light sedation	Briefly (< 10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 5. Richmond Agitation-Sedation Scale (RASS) *(continued)*

<table>
<tr><th>Score</th><th>Term</th><th>Description</th></tr>
<tr><td colspan="3">Procedure
1. Observe patient. Is patient alert and calm (score 0)? Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under <i>Description</i>)?
2. If patient is not alert, in a loud speaking voice, state the patient's name and direct the patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker. Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1). Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2). Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder. Patient has any movement to physical stimulation (score −4). Patient has no response to voice or physical stimulation (score −5).</td></tr>
</table>

Reprinted with permission from: American Thoracic Society. Copyright © 2014 American Thoracic Society. Sessler CN, Gosnell M, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002;166:1338-44. Official Journal of the American Thoracic Society.

Table 6. Riker Sedation-Agitation Scale

7	Dangerous agitation	Pulling at ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, trying to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

ETT = endotracheal tube.

Adapted with copyright permission from: Lippincott Williams and Wilkins/Wolters Kluwer Health. Simmons LE, Riker RR, Prato BS, et al. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation Agitation Scale. Crit Care Med 1999;27:1499-504.

L. Frequency of Screening and Technique Used for SBT

1. A randomized trial (FAST) using a 2×2 factorial design included patients that had been on the ventilator for at least 24 hours who could initiate spontaneous breaths and were on an FIo_2 of 70% or less and a PEEP of 12 or less. Patients were randomized to more frequent or once-daily trials using a T piece or an SBT lasting 30–120 minutes. There were 198 patients in the once-daily screening and pressure-supported SBT group, 204 in the the once-daily screening and T-piece SBT, 195 in the more frequent screening and pressure-supported SBT, and 200 in the more frequent screening and T-piece. SBT. The median time to successful extubation was 2 days (95% CI, 1.7–2.7) for once-daily screening and pressure-supported SBT, 3.1 days (95% CI, 2.7–4.8) for once-daily screening and T-piece SBT, 3.9 (95% CI, 2.9–4.7) for more frequent screening and pressure-supported SBT, and 2.9 (95% CI, 2.0–3.1) for more frequent screening and T-piece SBT. An interaction was found between screening frequency and SBT technique, which showed that more frequent screening and pressure-supported SBT increased the time to successful extubation (HR, 0.70 [95% CI, 0.50–0.96]; *P* = .02. Screening once-daily and pressure-supported SBT did not reduce the time to successful extubation (HR 1.3 [95% CI, 0.98–1.70]; P = .08).

M. Acute Withdrawal Syndrome of Long-term Analgesia and/or Sedation in the ICU

1. Patients who have been receiving high doses of continuous infusion sedation and/or analgesia in the ICU for an extended period may be at risk of sedative or analgesia withdrawal as dose tapering begins. In a retrospective review of adult trauma/surgical ICU patients, 32% of patients experienced either sedative or opiate withdrawal soon after discontinuing these medications. The patients in this study had been in the ICU for 20 days or more and were receiving higher mean daily analgesic and sedative doses than were the non-withdrawal patients (fentanyl 6.4 mg vs. 1.4 mg; lorazepam 38 mg vs. 11 mg). The withdrawal patients in this study were also more likely to have received an NMBA (Crit Care Med 1998;26:676-84).
2. Data: An international, multicenter, observational, point prevalence study in 229 adult ICUs showed that a small number of ICUs have policies or protocols for opioid or sedative weaning or iatrogenic withdrawal syndrome. Even when these protocols exist, they are rarely used.
3. The risk factors and incidence of sedation or analgesia withdrawal in adult ICU patients have not been well characterized; however, these are important considerations in the long-term ICU patient receiving high doses of these medications. Use of longer-acting agents given orally or by feeding tube has been described to assist in the transition off long-term continuous infusions. The medical indication and dosing plan for using oral medications to taper off continuous infusions should be clearly documented in the medical chart on patient discharge from the ICU. Clonidine is a potential consideration in patients to aid in dexmedetomidine withdrawal.

Patient Cases

3. A 48-year-old man with cirrhosis and now hepatorenal syndrome was intubated for respiratory distress. He has been receiving midazolam 1 mg/hour and fentanyl 75 mcg/hour for 2 days; his RASS (−4 to −5) and CPOT has been 1 for 24 hours. Oxygen requirements have decreased, and vital signs are normal. Which is the most appropriate change in his medications?
   A. Decrease midazolam; give as-needed lorazepam for agitated RASS score.
   B. Discontinue midazolam and fentanyl; give as-needed fentanyl for CPOT of 3 or greater.
   C. Discontinue midazolam; initiate propofol drip.
   D. Change midazolam to dexmedetomidine drip.

4. T.L. is a 55-year-old woman intubated for respiratory distress for severe pneumonia. She is receiving fentanyl 50 mcg/hour and dexmedetomidine 1.0 mcg/kg/hour. Her home medications are confirmed to include esomeprazole 20 mg daily, lorazepam 1 mg three times daily, and citalopram 10 mg daily. The nurse reports intermittent agitation with tachycardia and a negative pain score. Which is the most appropriate recommendation?
   A. Increase fentanyl drip for agitated RASS score.
   B. Reinitiate lorazepam and citalopram.
   C. Give fentanyl boluses as needed for agitation.
   D. Increase dexmedetomidine.

IV. DELIRIUM IN THE INTENSIVE CARE UNIT

A. Delirium is an acute and fluctuating disturbance in consciousness resulting in the inability to receive, process, store, or recall information. In the ICU, delirium may present as hyperactive (agitated and restless), hypoactive (flat affect, apathy, lethargy, decreased responsiveness), or mixed hyper/hypoactive states. Most common in the ICU are mixed and hypoactive states of delirium. Two screening tools are currently recommended by the PAD guidelines: (1) the CAM-ICU and (2) the ICDSC. Both the CAM-ICU and the ICDSC require a RASS (-2) or a SAS (3) or more alert to be completed.
   1. The CAM-ICU assesses four features: (1) acute change or fluctuation in mental status from baseline, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking. If features 1 *and* 2 plus feature 3 *or* 4 are present, the patient is considered positive for delirium. Detailed training is available at www.icudelirium.org.
   2. The ICDSC consists of eight items, evaluated during an 8- to 24-hour period. The eight symptoms are level of consciousness, inattention, disorientation, hallucinations-delusions-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbances, and symptom fluctuation. A point is given for any symptom that is present during the previous 24 hours; a score of 4 or higher indicates the presence of delirium.

B. Background – 30%–80% of ICU patients reportedly develop delirium, depending on the severity of illness and the diagnostic method, yet assessment for delirium is still not routine in most U.S. ICUs. During a patient's hospitalization, the presence of delirium is associated with difficulty in weaning mechanical ventilation and longer duration of mechanical ventilation, increased use of physical and chemical restraints, longer duration of ICU stay, and additional stress to family and friends who may not understand the course of delirium. Delirium is also associated with up to a 3-fold increase in mortality, increase in cognitive decline, delay in cognitive recovery, and increased likelihood of being discharged to a nursing home. Two studies found that a longer duration of delirium was independently associated with worse activity of daily living scores and worse cognitive impairment scores at 3 and 12 months post-ICU discharge (Crit Care Med 2014;42:369-77; N Engl J Med 2013;369:1306-16). A retrospective study reported increased difficulty in the weaning of mechanical ventilation when delirium was detected in patients during the first spontaneous weaning trial compared with in patients who did not have delirium (Respirology Nov 2015;1-8).

1. The underlying pathophysiology of delirium is not well understood; however, it may involve a complex set of factors:
    a. Cerebral hypoperfusion and alterations in cerebral blood flow
    b. Degradation of the blood-brain barrier, causing influx of inflammatory cytokines and microvascular thrombosis
    c. Depletion in central neurotransmitters (e.g., dopamine, norepinephrine, serotonin)
    d. Depletion in acetylcholine
    e. Medication withdrawal
2. Risk factors for delirium: A systematic review of studies from 2001 to 2013 described 11 variables identified as risk factors for developing delirium in the ICU, extracting from only a strong or moderate level of evidence (Crit Care Med 2015;43:40-7):
    a. Age
    b. Preexisting dementia
    c. History of baseline hypertension
    d. Sedative-associated coma
    e. APACHE II (Acute Physiology and Chronic Health Evaluation II) score
    f. Delirium on the previous day
    g. Emergency surgery
    h. Mechanical ventilation
    i. Organ failure
    j. (Poly)trauma
    k. Metabolic acidosis
3. Other reported risk factors or precipitants:
    a. Infection
    b. Dehydration or malnutrition
    c. Sleep deprivation
    d. Centrally acting medications (benzodiazepines, opiates, anticholinergics)
    e. Lack of exposure to sunlight
    f. Lack of personal interaction
    g. Physical restraints or insertion of catheters or tubes
4. Medication-induced altered mental status – Although the development of delirium is considered multifactorial, any patient who presents with a change in mental status should have his or her medications and doses immediately scrutinized as part of the initial workup for delirium. Several classes of medications have long been recognized for their effects on mental status and cognitive function, in or out of the ICU. These medications have the potential to affect a patient's level of consciousness or course of delirium at any point in the patient's hospital stay. Anticholinergics, benzodiazepines, opiates, antipsychotics, antispasmodics, anticonvulsants, corticosteroids, and others should be used with caution in a hospitalized patient, with close monitoring of the patient's cognitive adverse effects. Because renal and hepatic function may fluctuate throughout an ICU stay and affect the clearance of these medications, doses must be thoughtfully titrated. Research on the degree of impact these medications have on the overall course of sedation and delirium in the ICU is difficult to characterize,

and research is undergoing. Given the multifactorial nature of delirium in the ICU, clinicians should be leery of solely assigning blame to medications but should remain vigilant when assessing the need and doses of the aforementioned medications.

a. Benzodiazepines: The PADIS guidelines state "benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients." Of interest, research directed at finding an independent association between the use of benzodiazepines and the development of delirium in the ICU including a meta-analysis, a randomized trial, and a systematic review has yielded mixed results (Crit Care Med 2015;43:40-7; Crit Care Med 2015;43:557-66; Crit Care Med 2013;41:S30-8). Investigators used more appropriate statistical analysis for a fluctuating illness such as delirium (e.g., Markov monitoring was used to determine the probability of a daily transition to delirium while assuming this was independent of the patient history beyond the prior day) in addition to more frequent delirium monitoring to examine the use of benzodiazepines and the transition from an awake state without delirium to delirium, or from coma to delirium by the next day (Intensive Care Med 2015;41:2130-7). This study found that a midazolam equivalent dose of just 5 mg/day increased the odds of developing delirium the next day by 4%, and the use of benzodiazepine infusions was an independent risk factor for the transition to delirium in the study population. However, there was a large difference in the daily dose of benzodiazepines between the continuous infusion (daily median dose 99 mg) compared with the intermittent dosing group (daily median dose 4.1 mg), bringing into question whether the risk factor for the transition to delirium was indeed the cumulative dose and not the method of administration. As the data evolve, the scrutiny of benzodiazepine use should persist for ICU clinicians. Routine strategies to preferentially use a non-benzodiazepine sedative (e.g., propofol or dexmedetomidine) and to avoid benzodiazepine infusions unless clinically indicated should be used in addition to diligent performance of daily SATs to discontinue use as soon as possible.

b. Anticholinergics: These medications are known for their sedating and altering effects on mentation and should be avoided or used with extreme caution in the ICU setting. One proposed mechanism for delirium is a decline in acetylcholine concentrations; therefore, any medication that may further inhibit the activity of acetylcholine could worsen the patient's mental status. A prospective cohort study of 1112 critically ill patients was conducted to determine whether anticholinergic exposure increased the probability of transitioning to delirium. On 6% of ICU days, transition from "awake and without delirium" to "delirium" occurred. A nonsignificant increase in the probability of transitioning to delirium the following day resulted from a 1-unit increase in the Anticholinergic Drug Scale (odds ratio 1.05; 95% CI, 0.99–1.10). The dose of the medication was not evaluated to determine the effects on the transition to delirium, and it was not evaluated if patients were already delirious and remained delirious while receiving anticholinergic medications (Crit Care Med 2015;43:1846-52).

c. Systemic corticosteroids: The neuropsychiatric effects of systemic steroids in various clinical settings have been described for more than 50 years. Common symptoms include mania, depression, mood lability, anxiety, insomnia, delirium, and psychosis. The incidence of these symptoms varies greatly depending on the clinical setting, dose of steroid, and patient's underlying medical history. Reported risk factors for neuropsychiatric effects secondary to steroids include a daily prednisone dose equivalent to 40 mg or greater, hypoalbuminemia, underlying psychiatric disorder, and blood-brain barrier damage (Curr Opin Organ Transplant 2014;19:201-8). Although steroids are commonly used in the ICU for various indications and at various doses, significant research directed at the neuropsychiatric effects of steroids in the critically ill population is lacking. In a secondary analysis of a multicenter observational study of adult medical and surgical ICU patients with acute lung injury (n=330), Schreiber et al. found a significant and independent association between the use of systemic corticosteroids and the transition to delirium from a noncomatose, non-delirious state within 24 hours of corticosteroid administration (odds ratio [OR] 1.52 [1.05–2.21], p=0.03). Delirium was documented on one or more days in 83% of patients, with a median duration of 7 days. There was no significant association in prednisone-equivalent dose and transition to delirium. Schreiber et al. recognize that a direct causal relationship could not be determined between corticosteroid use and delirium from this observational study; however, they believe that the study adds valuable data toward our understanding of risk factors for delirium in the ICU (Crit Care Med 2014;42:1480-6). A second study that investigated steroids and transition to delirium in a mixed medical and surgical ICU population (n=1112) found no association between steroid use and a transition to delirium. The median prednisone equivalent dose was 50 mg (Crit Care Med 2015;43:e585-8).

5. Outcomes of sedation-related versus illness-related delirium: A single-center study using propofol and fentanyl timed its CAM-ICU assessments before and after a daily sedation interruption protocol. Rapidly reversible delirium was defined as delirium while patients were receiving sedation that resolved within 2 hours after performing an SAT. This type of delirium was rare (12% of the 102 patients), but these patients has a prognosis that was similar to patients who did not have delirium. Most patients (75%) had persistent delirium, delirium that did not resolve with cessation of sedatives, a higher risk of death, and longer length of stay (Am J Respir Crit Care Med 2014;189:658-65). Patients can have both sedation- and illness-related delirium, and additional research in this area is needed to clarify the differences in short- and long-term outcomes.

C. Monitoring for Delirium: SCCM recommends assessing critically ill patients for delirium with a validated tool such as either the CAM-ICU or the ICDSC. The PAD guidelines summarized their review of five delirium assessment scales used for adult ICU patients. The two scales with the highest psychometric (e.g., validity and reliability) scores were the CAM-ICU and the ICDSC. Both scales were designed for patients in the ICU either on or off mechanical ventilation, and both showed high sensitivity and specificity when tested against the American Psychiatric Association's criteria for delirium.

1. Delirium should be assessed at least every 8-12 hours and documented in the medical chart; results should be discussed with the medical team. Because these assessment scales cannot distinguish between sedation- and disease-related causes of delirium, delirium assessments should ideally be timed both before and after SATs with appropriate time allowed for drug clearance (www.icudelirium.org, Am J Respir Crit Care Med 2014;189:658-65). If this timing is not feasible and a patient screens positive for delirium while receiving ongoing analgesia or sedation, an SAT should be conducted if the patient passes the safety screen to assist in ruling out a medication-induced cause of delirium.
2. If a patient's delirium score is positive, the medical team should correct possible etiologies (e.g., decrease sedative doses, if safe), decrease ongoing risk factors, address inciting factors (e.g., metabolic derangements, infection, withdrawal), and try nonpharmacologic treatment and preventive measures when appropriate.

D. Prevention of Delirium: With a lack of data supporting the use of pharmacologic agents to prevent delirium, the PADIS guidelines suggest not using haloperidol, an atypical antipsychotic, dexmedetomidine, a statin, or ketamine to prevent delirium in critically ill patients. Instead, the recommendations are focused on nonpharmacologic prevention methods when feasible, particularly for patients at high risk of delirium. Preventive efforts may help avert 30%–40% of new-onset delirium cases, particularly in older adults. Recommended nonpharmacologic strategies by the PADIS guidelines include:

1. Performing rehabilitation or mobilization in critically ill adults
2. Using a multicomponent intervention to reduce or shorten delirium (e.g., reorientation, cognitive stimulation, use of clocks); improve sleep (e.g., minimize light and noise); improve wakefulness (i.e., reduce sedation); reduce immobility (e.g., early rehabilitation/mobilization); and reduce hearing and/or visual impairment (e.g., enable use of devices such as hearing aids or eyeglasses).

3. Decreasing the use of benzodiazepines and anticholinergics in patients at risk of delirium; use the lowest effective doses of any sedating medication (e.g., opiates, antipsychotics).
4. REDUCE was a randomized, double-blind, placebo-controlled study of 1789 critically ill patients randomized to prophylactic haloperidol 1 mg, haloperidol 2 mg, or placebo. The 1-mg haloperidol group was prematurely stopped because of futility (JAMA 2018;319:680-90). No difference occurred in the median days that patients survived in 28 days in the 2-mg haloperidol group compared with 28 days in the placebo group (95% CI, 0-0; p=0.93) with a hazard ratio of 1.003 (95% CI, 0.78–1.30; p=0.82). None of the 15 secondary outcomes were statistically different between the three groups. These outcomes included delirium incidence (mean difference 1.5%; 95% CI, −3.6% to 6.7%), delirium- and coma-free days (mean difference 0 days; 95% CI, 0–0 days), and duration of mechanical ventilation, ICU, and hospital length of stay (mean difference 0 days; 95% CI, 0–0 days for all three measures). Adverse events did not differ between groups.

E. Sleep in the ICU: Uninterrupted sleep (ideally 4 hours or more) is vital for an adequate immune response to illness, to maintain normal metabolic and hormonal balance, and to help decrease delirium and/or agitation. Disturbances in the ICU such as multiple alarms and frequent physical interruptions (e.g., examination, turning, laboratory tests, medication administration) make it challenging for patients to maintain the slow-wave sleep cycle needed for optimal immune function. Sleep research in the ICU is ongoing, and more information will be forthcoming regarding its effects in the critically ill patient. The PADIS guidelines suggest not routinely using physiologic sleep monitoring clinically in critically ill adults. In addition, the PADIS guidelines suggest not using aromatherapy, acupressure, or music at night to improve sleep in critically ill adults. However the PADIS guidelines do suggest using noise and light reduction strategies to improve sleep in critically ill adults. The PADIS guidelines make no recommendation regarding the use of melatonin to improve sleep or regarding the use of dexmedetomidine at night to improve sleep. The PADIS guidelines suggest not using propofol to improve sleep in critically ill adults. In addition, the PADIS guidelines suggest using a sleep-promoting, multicomponent protocol in critically ill adults.
   1. To avoid waking patients at night, pharmacists should ensure that medications are scheduled during the daytime and evening hours, if possible—particularly orally or subcutaneously administered medications.
   2. Sleep protocols should seek to cluster patient care activities (e.g., vital sign checks, radiology tests, laboratory checks, sedation assessments) around nighttime sleeping hours unless clinically indicated in a specific patient population.
   3. A two-center, double-blind randomized trial randomized 100 critically ill adults without delirium to nocturnal dexmedetomidine or placebo (Am J Respir Crit Care Med 2018;197:1147-56). During the ICU stay, nocturnal dexmedetomidine was associated with a greater proportion of patients who remained delirium free (dexmedetomidine (40 of 50 patients [80%]) than with placebo (27 of 50 patients [54%]; relative risk 0.44; 95% CI, 0.23–0.82; p=0.006). Adverse events did not differ between the two groups.

F. Treatment of Delirium: The cause of delirium may be multifactorial, and identifying and correcting the underlying etiology is the first step in management. Patients can also progress to alcohol withdrawal or withdrawal from other chronic medications/substances and present with hyperactive delirium. The PADIS guidelines suggest not using an atypical antipsychotic, haloperidol, or a statin to treat subsyndromal delirium or delirium (N Engl J Med 2018;379:2506-16). The Modifying the Impact of the ICU-Associated Neurological Dysfunction-USA (MIND USA) Study is a multicenter, randomized, placebo-controlled study of 566 patients showing that haloperidol and ziprasidone did not reduce delirium, time on the ventilator, ICU or hospital length of stay, or death compared with placebo. Arrhythmias, parkinsonism (extrapyramidal symptoms), neuroleptic malignant syndrome, study drug discontinuation, and other safety concerns were extremely low across all three groups. Additionally, a planned secondary analysis of the MIND USA study showed that neither haloperidol nor ziprasidone significantly increased QTc intervals compared with placebo. The AID-ICU trial was a multicenter, randomized, placebo-controlled trial of 963 patients with delirium randomized to haloperidol or placebo. The mean number of days alive and out of the hospital was 35.8 (95% CI, 32.9–38.6) in the haloperidol group and 32.9 (95% CI, 29.9–35.8) in the placebo group with an adjusted mean difference of 2.9 days (95% CI, -1.2 to 7; p=0.22). Antipsychotics remain viable for the short-term control of agitation (e.g., alcohol or drug withdrawal) or severe anxiety with the need to avoid respiratory suppression (e.g., heart failure, COPD, or asthma). If an antipsychotic is initiated, low starting doses should be considered, and daily review of drug interactions, adverse effects, dosing titration, and need for the antipsychotic should be completed. In addition, a strategy for discontinuation or outpatient follow-up should be documented to help avoid inadvertent continuation beyond the hospital environment (Table 7). Serious adverse effects are associated with the use of any antipsychotic; effects such as arrhythmias, serotonin syndrome, neuroleptic malignant syndrome, extrapyramidal symptoms, and oversedation should be closely monitored on a daily basis. Dose ranges for atypical antipsychotics for ICU delirium are not well described. The American Geriatrics Society 2015 Beers Criteria for medication use in older adults includes the following recommendation: “Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options have failed or are not possible AND the older adult is threatening substantial harm to self or others.” If the ICU team decides to use antipsychotics in older adults, lower starting doses should be considered, together with daily review of drug interactions and adverse effects. The PADIS guidelines suggest using dexmedetomidine for delirium in mechanically ventilated adults when agitation precludes weaning/extubation. The PADIS guidelines suggest not using bright light therapy to reduce delirium in critically ill adults.

G. Inadvertent Continuation of Antipsychotics Beyond ICU Discharge: The PADIS guidelines discuss the use of adjunctive medications for ICU patients (e.g., antipsychotics, gabapentin, carbamazepine). Although their use in the ICU may be appropriate, there is a potential for inadvertent continuation of these medications on hospital discharge if a treatment plan is not clear in the medical record. This has been a well-documented problem with other medications initiated in the ICU (e.g., histamine receptor blockers, proton pump inhibitors), and studies have been published describing the continuation of newly prescribed antipsychotics from the ICU and hospital, even when an indication for continuation was not documented (J Crit Care 2015;30:814-6; J Crit Care 2016;33:119-24). Continued use of these medications beyond the hospital stay could lead to serious adverse effects, drug interactions, and significant drug cost as well as a presumption of a psychiatric or neuromuscular disorder associated with these drugs. Communication to the next direct patient care provider is crucial to appropriately direct the next steps in medication reconciliation.

Table 7. Antipsychotics[a]

Drug	CYP Substrate (major)	Usual Starting Dose	Significant Adverse Effects[b]	Formulations
Haloperidol	3A4, 2D6	1–2 mg older adults; 2–4 mg if history of psychiatric disorders	Anticholinergic: * Sedation: * EPS: ** NMS: *	PO, IM, IV
Olanzapine	1A2	5 mg	Anticholinergic: ** Sedation: ** EPS: * NMS: * Neuromuscular weakness	PO, disintegrating tablet, IV, IM
Quetiapine	3A4	12.5–25 mg	Anticholinergic: ** Sedation: ** NMS: * Orthostatic hypotension: **	PO
Risperidone	2D6	0.5–1 mg	Anticholinergic: * Sedation * EPS: ** NMS: * Orthostatic hypotension: ** Cardiac conduction abnormalities	PO, disintegrating tablet
Ziprasidone	1A2 (minor) 3A4 (minor)	20 mg PO; 10 mg IM	Anticholinergic: * Sedation: * EPS: * NMS: *	Oral, IM

NOTE: * = lower risk; ** = medium-higher risk

[a] Not all medications listed are FDA label approved for use in delirium; not all are recommended by SCCM for the treatment of delirium in the ICU.

[b] Adverse effects other than QTc prolongation. Documented QTc prolongation incidence: IV haloperidol = ziprasidone > risperidone > olanzapine = quetiapine.

EPS = extrapyramidal symptoms; IM = intramuscular(ly); IV = intravenous(ly); NMS = neuroleptic malignant syndrome; PO = oral(ly)

1. Haloperidol (Haldol): Available in oral, intravenous, and intramuscular injection dosage forms
   a. Pharmacokinetics: Hepatically metabolized to inactive metabolites, renally cleared. Many drug CYP3A4 and 2D6 substrate. Peak plasma concentrations for oral about 6 hours for oral and 20 minutes for intramuscular.
   b. Suggested starting dose for ICU delirium: 2–5 mg as needed
   c. Adverse effects (early onset): Cardiac arrhythmias, anticholinergic effects, extrapyramidal symptoms
2. Quetiapine (Seroquel): A randomized, placebo-controlled pilot trial compared the efficacy and safety of scheduled quetiapine with placebo for the treatment of delirium in ICU patients during a 10-day study (Crit Care Med 2010;38:419-27). Significant exclusions were as follows: patients with end-stage liver disease, those with alcohol withdrawal, those with a QTc greater than 500, and those receiving concomitant QTc-prolonging agents. This small pilot study (n=36), in which the placebo group was administered as-needed intravenous haloperidol, found that quetiapine was associated with a shorter time to first resolution of delirium, reduced duration of delirium, and less agitation than placebo. Mortality and ICU length of stay were not different from placebo.
   a. Pharmacokinetics: Hepatically metabolized to one active and two inactive metabolites. Metabolites renally cleared. Many drug interactions, CYP3A4 (major) and CYP2D6 (minor) substrates. Peak plasma concentrations for oral about 1½ hours (immediate release).

   b. Initial dose range for ICU delirium: 50 mg one to three times daily. Consider lower starting doses for older adult patients because of sedating effects. The Devlin study initiated 50 mg every 12 hours and titrated to a maximum dose of 200 mg every 12 hours.
   c. Adverse effects (early onset): Sedation, orthostatic hypotension, extrapyramidal symptoms, QTc prolongation

3. Olanzapine (Zyprexa): Available in oral, orally disintegrating, and intramuscular (immediate and extended release) dosage forms. Intramuscular administration may result in plasma concentrations 5 times those of oral administration. The immediate release intramuscular formulation can also be administered intravenously. The U.S. Food and Drug Administration (FDA) warns that the use of intramuscular olanzapine has resulted in unexplained deaths; use of intramuscular olanzapine with benzodiazepines may result in significant oxygen desaturation.
   a. Pharmacokinetics: Metabolized by glucuronidation and CYP 1A2, 2D6 oxidation. Clearance is significantly increased (around 40%) in smokers and decreased in females (around 30%). Many drug interactions, CYP1A2 (major) and CYP2D6 (minor) substrates. Weak inhibitor of several CYP isoenzymes. Peak plasma concentrations for oral: About 6 hours.
   b. Suggested starting dose for ICU delirium: 5 mg orally once daily
   c. Adverse effects (early onset): Drowsiness, extrapyramidal symptoms, neuromuscular weakness, serotonin syndrome. High doses may cause cardiac arrhythmias, cardiopulmonary arrest, and extreme sedation to coma-like states.
4. Risperidone (Risperdal): Available in oral and oral dispersible tablets (M-tabs) and intramuscular injection dosage forms
   a. Pharmacokinetics: Hepatically metabolized to active metabolites, renally cleared. Many drug interactions, CYP2D6 (major) and CYP3A4 (minor) substrates and P-glycoprotein. Peak plasma concentrations for oral about 1 hour.
   b. Suggested starting dose for ICU delirium: 0.25–0.5 mg once or twice daily
   c. Adverse effects (early onset): Cardiac arrhythmias, anticholinergic effects, extrapyramidal symptoms
5. Ziprasidone (Geodon): Studied in a multicenter, randomized, placebo-controlled pilot trial of mechanically ventilated patients to test the hypothesis that antipsychotics would improve days alive without delirium or coma in the ICU (MIND trial). Medical and surgical adult ICU patients (n=101) from six tertiary-care centers in the United States on mechanical ventilation who had an abnormal level of consciousness or were receiving analgesia/sedative medications were randomly assigned to receive haloperidol, ziprasidone, or placebo every 6 hours for up to 14 days during a 21-day study. During the study, no difference was found in median days alive without delirium or coma between the haloperidol (14 days), ziprasidone (15 days), and placebo (12.5 days) groups, p=0.66. The study also found no difference in ventilator-free days, hospital length of stay, or mortality among the three groups (Crit Care Med 2010;38:428-37).
   a. Ziprasidone is available in oral and intramuscular dosage forms.
   b. Pharmacokinetics: Hepatic by glutathione and aldehyde oxidase. Minor substrates of CYP 1A2, 3A4. Peak plasma concentrations for oral about 6 hours; intramuscular about 1 hour.
   c. Suggested starting dose for ICU delirium: 20 mg twice daily (oral)
   d. Adverse effects (early onset): Somnolence, extrapyramidal symptoms, dizziness, orthostatic hypotension

V. ABCDEF BUNDLE

A. Incorporating multiple concomitant patient care interventions into one consolidated bundle may be an effective strategy to improve clinical outcomes in critically ill patients. SCCM recommends implementing the "ABCDEF" bundle to align and coordinate care using an interprofessional approach (e.g., physician, nursing, pharmacy, respiratory therapy, physical and occupational therapy). The following practice principles are applied to the bundle:
   1. A: Assess, prevent, and manage pain
   2. B: Both SATs and SBTs
   3. C: Choice of analgesia and sedation
   4. D: Delirium: Assess, prevent, and manage
   5. E: Early mobility and exercise
   6. F: Family engagement and empowerment.

B. Assess, Prevent, and Manage Pain ("A" of the bundle): Asking the patient to self-report pain or to use the CPOT or BPS if the patient is nonverbal. Preventing pain by recognizing patients with known sources of pain (i.e., rib fractures) and scheduling analgesics when indicated. Managing pain by ordering the most appropriate pharmacologic agent on the basis of the source of pain and renal and liver function.

C. Daily coordination of the SAT with the SBT ("B" of the bundle) versus usual care with the SBT has been shown to significantly decrease the time on mechanical ventilation and ICU length of stay in randomized studies. This was reviewed earlier in the chapter in the Agitation section.

D. Choice of Sedation ("C" of the bundle): Use a multidisciplinary approach, including focused pharmacy input, to choose a sedative according to individual patient needs, hemodynamic stability, and organ function (e.g., hepatic, renal, cardiac, pulmonary, pancreatic).

E. Delirium Assessment, Prevention, and Management ("D" of the bundle): Regularly assess for delirium using the CAM-ICU or the ICDSC every 8–12 hours. Use delirium preventive measures in all patients when safe to do so.

F. Early Mobility ("E" of the bundle): Perform a mobility safety screen, and implement a daily mobility protocol.

G. Family Engagement and Empowerment ("F" of the bundle): Good communication with the family is critical at every step of the patient's clinical course, and empowering the family to be part of the team to ensure best care is adhered to diligently will improve many aspects of the patient's experience.

H. In a prospective, multicenter, cohort study from 68 academic, community, and federal ICUs during a 20-month collection period, performance of the complete ABCDEF bundle was associated with a lower likelihood of death within 7 days (HR 0.32; CI, 0.17–0.62), next-day mechanical ventilation (OR 0.28; CI, 0.22–0.36), coma (OR 0.35; CI, 0.22–0.56), delirium (OR 0.60; CI, 0.49–0.72), physical restraint use (OR 0.37; CI, 0.30–0.46), ICU readmission (OR 0.54; CI, 0.37–0.79), and discharge to a facility other than home (OR 0.64; CI, 0.51–0.80). There was a dose response in between higher proportional bundle performance and improvement in each clinical outcome ($p<0.002$). Pain was more commonly reported as bundle performance increased ($p=0.0001$), probably because more patients were awake.

VI. POST-INTENSIVE CARE SYNDROME

A. Advances in critical care have decreased mortality and resulted in an increased likelihood of surviving critical illness. Post-intensive care syndrome (PICS) describes new or worsening impairments in physical, cognitive, or mental health status after critical illness and persisting beyond acute care hospitalization. Physical impairments include both pulmonary dysfunction and neuromuscular weakness. Impairments in memory and executive functioning are examples of cognitive dysfunction. Mental health impairments include depression, posttraumatic stress disorder, and anxiety. Medication management including glucose control, use of the ABCDEF bundle, and review of medication lists at every transition of care are important roles of the pharmacist to prevent PICS. Family members can also have PICS, termed PICS-F, in which these individuals have depression, posttraumatic stress disorder, anxiety, and prolonged grief. SCCM has taken progressive steps to help clinicians and families recognize the prolonged PICS and PICS-F through THRIVE. The establishment of an ICU follow-up clinic is one proposed method to manage long-term complications of patients with PICS and family members of PICS-F through optimization of physical, cognitive, and mental health; improved coordination of care; and reduction in health care use. The pharmacist should be considered a key member of the PICS clinic team who performs complete medication management on all patients seen in the clinic.

1. Physical impairment: A prospective, longitudinal study of 109 survivors with ARDS was conducted. Median (Interquartile Range) Total Lung Capacity (TVC) was 92% (77-97%), 92% (82–101%), and 95% (81–103%) of predicted value, respectively, at 1, 6, and 12 months after ICU discharge. Forced expiratory volume in 1 second (FEV_1) was 75% (58–92%), 85% (69–98%), and 86% (74–100%) of predicted value, respectively, at 1, 6, and 12 months after ICU discharge. Six-minute walk test was 49%, 64%, and 66% of predicted value, respectively, at 1, 6, and 12 months after ICU discharge. These 109 survivors of ARDS were further analyzed annually up to 5 years after ICU discharge. TVC was 94% (84–108%), 93% (78–107%), 92% (79–104%), and 94% (78–105%) of predicted value, respectively, at 2, 3, 4, and 5 years after ICU discharge. FEV_1 was 87% (75–99%), 79% (66–97%), 85% (68–98%), and 83% (69–98%) of predicted value, respectively, at 2, 3, 4, and 5 years after ICU discharge. Six-minute walk test was 68%, 67%, 71%, and 76% of predicted value, respectively, at 2, 3, 4, and 5 years after ICU discharge.
2. Cognitive impairment: A large, multicenter, prospective observational cohort study of 821 adult medical ICU and surgical ICU patients (called the BRAIN-ICU study) estimated the prevalence of long-term cognitive impairment after critical illness secondary to respiratory failure, cardiogenic shock, or septic shock (N Engl J Med 2013;369:1306-16). Delirium was the strongest independent predictor of cognitive impairment in the 50% of patients after critical illness. A Repeatable Battery for Neuropsychological Status (RBANS) score similar to Alzheimer disease (2 standard deviations below the population mean) was found in 26% of patients, and a score similar to moderate traumatic brain injury (1.5 standard deviations below the population mean) was found in 40% of patients 3 months after discharge. Both young and older adults, with and without comorbidities, experienced these deficits, which persisted at 12 months in 24% and 34% of these individuals having RBANS scores similar to Alzheimer disease and moderate traumatic brain injury, respectively.
3. Mental health impairments: A multicenter, prospective observational cohort study of 821 adult medical ICU and surgical ICU patients estimate the prevalence of depression, posttraumatic stress disorder (PTSD), and functional disability after critical illness secondary to respiratory failure, cardiogenic shock, or septic shock. Depression was found in 149 patients (37%) and 116 patients (33%) at 3 and 6 months after ICU discharge, respectively. Disabilities in basic activities of daily living were found in 139 patients (32%) and 102 patients (23%) at 3 and 6 months after ICU discharge, respectively. Disabilities in instrumental activities of daily living were found in 108 patients (26%) and 87 patients (23%) at 3 and 6 months after ICU discharge, respectively. PTSD was found in 27 patients (7%) at 3 and 6 months after ICU discharge.

4. A prospective, observational feasibility study was conducted at an academic hospital between July 2012 and December 2015 (Crit Care 2018;46:141-8). Patients were identified if at high risk of PICS; if so, post-ICU care was offered. Sixty-two patients were seen in the clinic. Median time from hospital discharge to ICU recovery center visit was 29 days. Cognitive impairment was identified in 64% of patients. Anxiety and depression were identified in 37% and 27% of patients. One-third of the patients were unable to ambulate independently. The median 6-minute walk distance was 56% of predicted. Only seven of the previously working patients (15%) had returned to work. Referral services and case management were provided 142 times. The median number of pharmacy interventions per patient was four.

B. Medication Management
1. Glucose dysregulation: A retrospective study of 74 patients with ARDS found that a blood glucose value of 153.5 mg/dL resulted in a 2.9 greater chance of developing cognitive impairment. A second retrospective case-control study of 37 surgical ICU patients with at least one episode of hypoglycemia found that cognitive impairment was higher in the hypoglycemic group ($p<0.01$). Intensive insulin therapy (maintaining blood glucose levels between 80 and 100 mg/dL) in surgical ICU patients decreased neuropathy from 51.9% to 28.7%, and the prevalence of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) from 49% to 25% in surgical ICU patients ($p<0.0001$) (Neurology 2005;64:1348-53). Intensive insulin therapy also decreased CIP and CIM from 51% to 39% in the medical ICU ($p=0.02$) in patients who had an ICU stay of at least 1 week. The percentage of patients needing mechanical ventilation for at least 2 weeks was reduced from 42% to 32% in the surgical ICU ($p=0.04$) and from 47% to 35% in the medical ICU ($p=0.01$). Subsequently, NICE-SUGAR showed increased mortality in the intensive insulin group (81 to 108 mg/dL) (27.5%) versus conventional glucose control (less than 180 mg/dL) (24.5%) ($p=0.02$). The SCCM guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients suggests that a blood glucose of 150 mg/dL or greater initiates interventions to maintain blood glucose less than 180 mgdL and to avoid hypoglycemia based off the results of NICE-SUGAR.
2. Continuation of inappropriate medications: The frequency of prescribed potentially inappropriate medications (PIMs) and actually inappropriate medications (AIMs) was evaluated in a single-center study of 120 older adult ICU survivors. PIMs were defined as potentially harmful on the basis of prior studies and pharmacologic effects. PIMs could further be classified as AIMs if the benefit of the drug was considered less than the harm. The 2003 Beers Criteria and medication safety data published since 2003 were used to identify medications (Arch Intern Med. 2011;171:1032-4). Medications were identified at five points during the hospital stay: admission, ward admission, ICU admission, ICU discharge, and hospital discharge. The most common categories of PIMs identified at hospital discharge were opioids, anticholinergic medications, antidepressants, and drugs causing orthostasis. Thirty-six percent of these PIMs were considered AIMs. The PIM categories at hospital discharge with the highest positive predictive values for being AIMs were anticholinergics (55%), nonbenzodiazepine hypnotics (67%), benzodiazepines (67%), atypical antipsychotics (71%), and muscle relaxants (100%). In multivariate analysis, the number of discharge PIMs was independently predicted by the number of preadmission PIMs ($p<0.001$), discharge to somewhere other than home ($p=0.03$), and discharge from a surgical service ($p<0.001$). Almost two-thirds of AIMs were initiated in the ICU.
3. Not restarting home medications: A large population-based Canadian cohort study of 396,380 patients evaluated records of hospital and outpatient medications prescribed from at least one of five of the following groups: (1) statins, (2) antiplatelet/anticoagulant agents, (3) levothyroxine, (4) respiratory inhalers, and (5) gastric acid–suppressing drugs. Patients were divided into three groups: hospitalization with an ICU admission, hospitalization without ICU admission, and nonhospitalized patients who served as the control group. Compared with control patients, those admitted to a hospital without an ICU stay were more likely to have medications discontinued among all five of the medication groups.

Patients admitted to a hospital with an ICU stay were also more likely to have medications discontinued among all five of the medication groups than were control patients. Except for respiratory inhalers, there was a higher risk of medication discontinuation in all medication groups in patients hospitalized with an ICU admission than in patients hospitalized without an ICU admission. The composite outcome of death, hospitalization, and emergency department visit up to 1 year after hospital discharge in all study patients was higher in patients in whom a statin or antiplatelet or anticoagulant was discontinued (JAMA. 2011;306:840-7).

4. A prospective, observational cohort study was conducted of all outpatient appointments of a tertiary care hospital's post-ICU clinic between July 2012 and December 2015. The pharmacist completed medication reconciliation, interview, counseling, and resultant interventions during the post-ICU clinic appointment. The pharmacist did a full medication review in 56 of the patients (90%). All 56 patients had at least one pharmacy intervention. Medications were discontinued at the clinic appointment for 22 of the patients (39%). New medications were initiated in 18 of the patients (32%). An adverse drug event was identified in nine of the patients (18%). Adverse drug event preventive measures were implemented in 18 patients (32%). Thirteen patients (23%) had an influenza vaccination administered. Two patients (4%) received a pneumococcal vaccination (Ann Pharmacother 2018;52:713-23).
5. A prospective, observational study was conducted in 12 ICUs/post-ICU clinics between September 2019 and July 2021. A full medication review was performed in 472 patients by a pharmacist at the post-ICU clinic.. In 397 (84%) patients, pharmacy interventions were made. Medications were stopped in 124 (26%) and started in 91 (19%) patients. The number of patients that had a dose decreased was 51 (11%). The number of patients that had a dose increased was 43 (9%). Adverse drug event (ADE) preventive measures were initiated in 115 (24%) patients. Identification of ADEs occurred in 69 (15%) patients. In 30 (6%) patients, medication interactions were identified.

Patient Cases

5. T.L. (from question 4) was extubated 24 hours ago, is currently receiving dexmedetomidine 0.2 mcg/kg/hour, and has received two doses of fentanyl 25 mcg over 24 hours for pain. She is alert and calm with intermittent periods of agitation. Her pain score is now negative, and she is newly positive for delirium by CAM-ICU. Her laboratory values and vital signs are normal. Which would best be recommended for the management of delirium?
   A. Continue dexmedetomidine, and start quetiapine for delirium.
   B. Discontinue dexmedetomidine, and increase maintenance fluids for dehydration.
   C. Discontinue dexmedetomidine, and order patient mobility as tolerated.
   D. Continue dexmedetomidine, and schedule oxycodone sustained release every 12 hours.

6. P.V. is a 70-year-old woman intubated for severe respiratory failure (F_{IO_2} 80%) and refractory shock from methicillin-resistant *Staphylococcus aureus* pneumonia, for which she was administered antibiotics, vasopressors, and steroids. She is on day 5 of mechanical ventilation (F_{IO_2} 50%) and has been off vasopressors for 48 hours. The nurse describes PAD, but the patient denies pain. Medications include vancomycin 1000 mg daily, heparin 5000 units subcutaneously every 12 hours, hydrocortisone 50 mg every 6 hours, and fentanyl 75 mcg/hour. Which is the most appropriate recommendation at this time?
   A. Increase fentanyl, and add midazolam for agitation.
   B. Decrease fentanyl, and discontinue hydrocortisone.
   C. Decrease fentanyl, and add haloperidol for delirium.
   D. Increase fentanyl, and change vancomycin to linezolid.

VII. NEUROMUSCULAR BLOCKADE IN THE INTENSIVE CARE UNIT

A. The most recent SCCM guidelines for the sustained use of neuromuscular blockade in the ICU were published in 2016. Surveys have reported a dramatic decrease in the use of NMBAs during the past 20 years, from around 80% to 15% in patients on mechanical ventilation (Crit Care Med 2016;44:2079-103). This change in practice may be secondary to a better understanding of the serious adverse effects of prolonged paralysis, together with accepted standards of care for modes of mechanical ventilation in patients with ARDS.

B. Clinical Scenarios for the Use of NMBAs in the ICU May Include:
   1. Rapid sequence intubation
   2. ARDS
   3. Status asthmaticus
   4. Elevated ICP
   5. Elevated intra-abdominal pressure
   6. Targeted temperature management after cardiac arrest

C. Acute Respiratory Distress Syndrome
   1. Cisatracurium has been the most-studied NMBA for ARDS since 2000, primarily as short-term treatment and in severe cases of ARDS. In 2010, a randomized placebo-controlled trial (n=340) found that short-term fixed-dose cisatracurium (48 hours) significantly improved 90-day survival, increased ventilator-free days, increased organ dysfunction–free days, and decreased barotrauma in patients with severe ARDS (Pao_2/Fio_2 less than 120 mm Hg). The investigators found no difference in neuromuscular weakness compared with placebo. Other cisatracurium studies have shown improvements in oxygenation and a reduction in inflammatory mediators.
   2. In retrospective studies, the use of NMBAs in ARDS was associated with a prolonged duration of mechanical ventilation, prolonged ICU length of stay, and increased mortality.
   3. Protective mechanisms of NMBAs in severe ARDS: Researchers have proposed mechanisms by which an NMBA may protect the lung against further injury in severe ARDS. These mechanisms are not completely understood, but they may help explain the beneficial effects of NMBAs in early, severe ARDS:
      a. Provide improved adaptation to the ventilator through increased thoracopulmonary compliance.
      b. Increase functional residual capacity, and decrease intrapulmonary shunt.
      c. Provide uniform distribution of pulmonary perfusion and pressures, favoring the perfusion of ventilated areas.
      d. Limit over-distention of high-compliance lung regions and recruit areas of smaller compliance.
      e. Decrease muscular oxygen consumption by decreasing ventilator asynchrony.
      f. Decrease production of proinflammatory cytokines in lungs and blood.
      g. Provide protective role against ventilator-induced trauma, including decreased incidence of pneumothoraces.
   4. The 2016 SCCM NMBA guidelines suggest that a NMBA be administered by continuous intravenous infusion early in the course of ARDS for patients with a Pao_2/Fio_2 of less than 150 mm Hg (weak recommendation). Use of NMBAs in ARDS remains controversial. Short-term use of cisatracurium (48 hours or less) when used early may be beneficial for severe ARDS (Pao_2/Fio_2 less than 120 mm Hg). The Reevaluation of Systemic Early Neuromuscular Blockade (ROSE) PETAL was a randomized, parallel-design study comparing cisatracurium with placebo for 48 hours on the effects of 90-day mortality. It was published after the guidelines and did not support using this early in course of ARDS.

D. Targeted Temperature Management After Cardiac Arrest
   1. The 2016 SCCM NMBA guidelines make no recommendation on the routine use of NMBAs for patients undergoing therapeutic hypothermia after cardiac arrest (insufficient evidence). They recommend use of a protocol that includes guidance on NMBA administration in patients undergoing therapeutic hypothermia (good practice statement).
   2. NMBAs have been used to prevent or treat shivering during therapeutic hypothermia.
   3. The optimal combination and dosing of sedatives and paralytics have not been well established because the metabolism of these drugs is significantly slowed during hypothermia, and potency may be decreased. NMBAs have been used in both a bolus and a continuous infusion fashion during therapeutic hypothermia.

E. Sedation During NMBA: The 2016 SCCM NMBA guidelines recommend that optimal clinical practice require administering analgesic and sedative drugs before and during neuromuscular blockade with the goal of achieving deep sedation (good practice statement). They also suggest that patients receiving a continuous infusion of NMBA should receive a structured regimen of physiotherapy (weak recommendation). It is critical that patients be in a sedated, non-agitated, and pain-free state before initiating an NMBA. Once the patient becomes paralyzed from the NMBA, the ability to accurately assess mental status or pain is ostensibly challenging and often unattainable. The deeper the degree of paralysis, the higher the risk of drug accumulation because nurses cannot routinely complete sedation interruption or taper to a lighter level of sedation. Common scenarios that slow the clearance of sedatives (e.g., hepatic and renal failure or a hypothermic state) can add to the likelihood of increased drug exposure and delayed awakening times once the paralytic and sedatives are discontinued. This risk of drug accumulation underscores the importance of a daily assessment for need of paralysis and frequent tapering of NMBA dosing once it is safe for the patient.

F. Two Classes of NMBAs According to Mechanism of Action: Depolarizing and Nondepolarizing:
   1. Depolarizing NMBAs: Bind and activate acetylcholine receptors, causing persistent depolarization, which then renders muscle fibers resistant to further cholinergic stimulation. Succinylcholine is the only available depolarizing NMBA. Because of its quick onset and short duration, it is commonly used for urgent or emergency intubation.
      a. Pharmacokinetics: Hydrolyzed by plasma pseudocholinesterase
      b. Usual dose: 0.05–1.5 mg/kg intravenously or intramuscularly
      c. Onset intravenously: 30–60 seconds; intramuscularly: 2–3 minutes
      d. Duration intravenously: 4–6 minutes; intramuscularly: 10–30 minutes
      e. Should not be used in patients with a history of malignant hyperthermia, hyperkalemia or risk factors for hyperkalemia (stroke, paralysis, or spinal, crush, or burn injuries after 24 hours), glaucoma, or penetrating eye injuries.
      f. Adverse effects: Arrhythmias, bradycardia or tachycardia, hyperkalemia, rhabdomyolysis
   2. Nondepolarizing NMBAs: Nicotinic receptor antagonists (competitive), blocking the action of acetylcholine at the neuromuscular junction. Divided into aminosteroid group (pancuronium, vecuronium, and rocuronium) and benzyl isoquinolinium group (atracurium, cisatracurium, doxacurium, and mivacurium).
      a. Pancuronium: Long-acting aminosteroid; intermittent or scheduled bolus may be preferred to continuous infusion because of accumulation and variable clearance. Older NMBA, not used much in the United States.
         i. Pharmacokinetics: Hepatically metabolized (30%–50%) and renally cleared as unchanged drug (50%–70%). Accumulation and prolonged duration of paralysis will occur with varying degrees of hepatic and/or renal dysfunction. Duration about 60–120 minutes.
         ii. Adverse effects: Vagolytic activity, sympathetic stimulation, bradycardia, prolonged effect

- b. Vecuronium: Intermediate-acting aminosteroid; often used as a continuous infusion
  - i. Pharmacokinetics: Hepatically metabolized (30%–50%); cleared renally (20%–30%), with fecal excretion. Has an active metabolite, around half the activity of parent compound. Duration 30 minutes after bolus intubation dose.
  - ii. Adverse effects: Vagolytic activity at higher doses, prolonged weakness
  - iii. Can be reversed with sugammadex by forming a complex that decreases the amount of vecuronium available to bind to nicotinic receptors in the neuromuscular junction.
- c. Rocuronium: An intermediate-acting aminosteroid; considered a suitable alternative to succinylcholine for rapid sequence intubation (dose: 0.6–1.2 mg/kg) because of its rapid onset of action (60–90 seconds). Duration 30–40 minutes.
  - i. Pharmacokinetics: Primarily hepatically metabolized, minimal renal excretion. No active metabolite. Prolonged effects have been observed in patients with hepatic or renal failure.
  - ii. Adverse effects: Vagolytic activity at higher doses, bradycardia
  - iii. Can be reversed with sugammadex by forming a complex that decreases the amount of rocuronium available to bind to nicotinic receptors in the neuromuscular junction.
- d. Atracurium: Intermediate-acting benzyl isoquinolinium; a mixture of 10 stereoisomers (contains 15% cisatracurium)
  - i. Pharmacokinetics: Undergoes Hofmann elimination to form the toxic metabolite laudanosine at high levels. Laudanosine is a cerebral stimulant that may precipitate seizure activity, clearance dependent on liver and kidney function. Duration of atracurium 20–40 minutes.
  - ii. Adverse effects: Histamine release may cause cardiovascular adverse effects and bronchospasm; laudanosine accumulation may cause seizure activity.
- e. Cisatracurium: An intermediate-acting benzyl isoquinolinium. Differences compared with atracurium: It is only one isomer, has a slower onset at normal bolus doses, no histamine release.
  - i. Pharmacokinetics: Undergoes Hofmann elimination, forms laudanosine but at much lower levels than atracurium. Renal and hepatic dysfunction do not alter cisatracurium clearance. Duration 30–60 minutes.
  - ii. Adverse effects: Prolonged weakness with continued use

G. Drug Interactions with NMBAs: Certain medications may decrease the activity of NMBAs, whereas others can enhance or prolong the paralytic action.

1. Drugs decreasing the activity of NMBAs:
   - a. Calcium: Antagonizes the effect of magnesium on neuromuscular blockade
   - b. Carbamazepine: Competitor of acetylcholine receptor
   - c. Phenytoin: Depressed postsynaptic response to acetylcholine
   - d. Ranitidine: Unknown mechanism
   - e. Theophylline: Unknown mechanism
2. Drugs prolonging the activity of NMBAs:
   - a. Antimicrobials: Aminoglycosides, clindamycin, tetracyclines, vancomycin. Decreases prejunctional acetylcholine release with decreased postjunctional acetylcholine receptor sensitivity; blocks acetylcholine receptor.
   - b. Cardiac medications: β-Blockers, calcium channel blockers, procainamide, quinidine, and furosemide. Decreases prejunctional acetylcholine release.
   - c. Immunosuppressants: Steroids (decrease end plate sensitivity to acetylcholine), cyclosporine (inhibits metabolism of certain NMBAs)

H. Choice of NMBA: Intermediate- to longer-acting agents such as vecuronium may be tried in bolus fashion initially before continuous infusion, particularly if organ dysfunction is present. The duration of paralysis for NMBAs cleared by Hofmann degradation may be more reliable when used as a continuous infusion because their clearance is not dependent on renal or hepatic function.

I. Train-of-Four (TOF) Monitoring and Dose Titration

1. The SCCM NMBA guidelines make no recommendation concerning the use of electroencephalogram-derived parameters (e.g., Bispectral Index [BIS], E-entropy, Cerebral State Index, and Patient State Index) as a measure of sedation during continuous NMBA administration (insufficient evidence). They suggest against the use of peripheral nerve stimulation (PNS) with TOF alone for monitoring the depth of neuromuscular blockade in patients receiving continuous NMBA infusions (very low quality evidence). They make no recommendation on the use of PNS to monitor the degree of block in patients undergoing therapeutic hypothermia (insufficient evidence). Typically, the goal of using an NMBA is to improve patient-ventilator synchrony and increase oxygenation. This may be achieved with varying degrees of paralysis and may not necessitate 100% block.
2. Monitoring the depth of neuromuscular blockade by peripheral nerve stimulators (e.g., TOF), together with measured oxygenation parameters, helps find the "lowest effective paralytic dose" and allows quicker recovery of spontaneous neuromuscular transmission once the NMBA is discontinued. Some clinicians do not believe that TOF monitoring is necessary and believe that using the clinical values alone is sufficient to determine NMBA dosing.
3. TOF delivers four supramaximal electrical impulses every 0.5 seconds to the ulnar, facial, or posterior tibial nerve. Response to the impulse is then measured by muscle twitches visualized from the associated innervated muscles (thumb or eye). Goals of paralysis can usually be reached with 2 or 3 of 4 twitches; 0 of 4 twitches indicates complete neuromuscular blockade, usually necessitating a decrease in NMBA dose. Oxygenation goals may be reached even with 4 of 4 twitches, indicating that the NMBA dose is effective and an increase is not warranted.
4. A baseline electrical current should be established before initiating an NMBA to determine how much electrical current is needed to produce a twitch. Usually 10–20 mA (amperage) is sufficient. The conduction of the electrical impulse may be dampened because of peripheral edema, loss of electrode adhesion, incorrect electrode placement, and hypothermia, which can lead to inaccurate readings. These factors should be reassessed with each use of the TOF.

J. Complications of NMBAs

1. Prolonged weakness: Several case reports associate the use of NMBAs and prolonged weakness, which could include myopathy, polyneuropathy, or neuromyopathy. Other risk factors may include concomitant use of corticosteroids, persistent hyperglycemia, and type of NMBA used. However, data are inconsistent and not controlled, and further studies are needed to clarify specific risk factors for prolonged weakness associated with NMBAs. Following a trend in creatine kinase concentration every 48–72 hours may help assess the presence of myopathy secondary to paralysis and prolonged immobilization. A creatine kinase concentration should not be solely relied on for the presence of myopathy, and daily determination of the need for the NMBA should still be considered, even with a normal creatine kinase.
2. Corneal abrasions: Paralysis eliminates the ability of the eyes to close and blink, increasing the risk of corneal ulcerations and infection. Prophylactic eye protection must be used in all patients on NMBAs (e.g., lubricating eye ointments or eye covers).
3. Thrombosis: Caused partly by immobility, patients receiving an NMBA may be up to 8 times more likely to have a DVT than those not on an NMBA. Prophylaxis for a DVT must be provided for all patients on an NMBA.

4. Awareness: Recent case reports document patient awareness during paralysis in the ICU. These patients report weird dreams, fear, resistance of restraints, thoughts of life and death, and pain. Patients must be deeply sedated before initiating an NMBA (Ann Emerg Med 2021;77:532-44).
5. Resistance to paralysis and/or potentiation: Certain disease states may produce an up-regulation in acetylcholine skeletal muscle receptors, leading to higher-than-normal doses of the NMBA (e.g., muscle trauma, muscle atrophy, burns). Acid-base disorders, electrolyte imbalances, and adrenal insufficiency may also cause unpredictable alterations in dosing requirements.
6. Anaphylaxis: Allergic reactions can occur after the first dose of an NMBA because the ammonium ions in NMBAs are commonly found in the household environment and in household products. If an allergic reaction is suspected, skin prick testing for the NMBA against a control can be done within 6 weeks of the reaction.

Patient Cases

7. A 55-year-old man intubated for severe ARDS (PaO_2/FIO_2 ratio less than 100 mm Hg) is receiving fentanyl 200 mcg/hour, midazolam 8 mg/hour, and propofol 40 mcg/kg/minute. He is deeply sedated but remains hypoxic and dyssynchronous with the ventilator after several changes in mechanical ventilation settings. Which is the most appropriate consideration at this time?
   A. Start scheduled lorazepam every 6 hours.
   B. Add quetiapine 50 mg every 8 hours.
   C. Change propofol to dexmedetomidine.
   D. Start a cisatracurium infusion.

8. A 70-year-old woman who is day 2 in the ICU is receiving a neuromuscular blocking agent (NMBA) and is sedated for severe ARDS. The TOF over 24 hours is 2 of 4 twitches at an amplitude of 10 mA. Arterial blood gas is pH 7.38, PCO_2 40 mm Hg, PO_2 91 mm Hg, and bicarbonate 24 mEq/L on 50% inspired oxygen and 10 cm H_2O PEEP; the patient is synchronous with the ventilator, and other clinical markers are stable. Which changes in management would be best to recommend?
   A. Decrease stimulator amplitude to decrease pain from excessive electrical current.
   B. Increase stimulator amplitude to test for more frequent twitches.
   C. Decrease the NMBA dose because the patient is clinically stable.
   D. Increase the NMBA dose until the TOF induces fewer twitches.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

This patient has a clear indication for intravenous pain medication from his recent trauma and multiple fractures. An "as-needed" opiate would likely not keep up with his pain control needs (Answers B and C are incorrect). His age and history of hypertension place him at risk of delirium; therefore, a benzodiazepine is not the best initial choice for this patient. A fentanyl infusion for pain with a propofol infusion if needed for sedation is the most appropriate answer (Answer A is incorrect; Answer D is correct).

2. **Answer: D**

Chest tube removal is specifically cited in the PADIS guidelines as an indication for both preemptive analgesia and nonpharmacologic relaxation techniques. This is given a "strong" recommendation, determining that the benefits outweigh the risks of preemptive therapy (Answer D is correct). Acetaminophen given just before the procedure will most likely not adequately treat pain associated with chest tube removal (Answer A is incorrect). Increasing an opiate infusion several hours before a bedside procedure can expose the patient to substantially higher amounts of drug than needed and cause delayed awakening times or other significant adverse effects from opiates (Answer C is incorrect). Extensive studies of appropriate preemptive analgesia for chest tube removal have not been completed; however, administering an opiate appropriately timed before manipulation of a chest tube is an accepted standard of therapy (Answer B is incorrect).

3. **Answer: B**

This patient has end-stage liver failure and acute renal failure; he will therefore not predictably clear midazolam or fentanyl infusions. With a RASS of −4 to −5, indicating no meaningful responsiveness to stimuli, all sedatives should be held if the patient is otherwise clinically stable to allow time for clearance of medications. If the patient was to develop pain based on a CPOT of 3 or more, then intermittent fentanyl is appropriate (Answer B is correct). A decrease in sedative dose or changing to a different sedative is not needed at this time based on the deeply sedated RASS score and would only further delay awakening time. Intermittent doses of benzodiazepines should avoided. (Answers A, C, and D are incorrect).

4. **Answer: B**

Withdrawal from certain home medications may occur if these medications are not reinitiated within a few days of admission. The onset of withdrawal symptoms will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication adherence to help identify drug withdrawal symptoms. Reinitiating these medications can be considered, unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PADIS guidelines discusses identifying and treating the etiology of agitation before adding other medications; reinitiating the benzodiazepine and antidepressant to treat withdrawal symptoms is the most appropriate answer (Answer B is correct). Neither fentanyl nor dexmedetomidine would treat withdrawal from a benzodiazepine or antidepressant (Answers A, C, and D are incorrect).

5. **Answer: C**

The PADIS guidelines stress using nonpharmacologic means to manage delirium when it is safe for the patient. Strong evidence for using dexmedetomidine to treat delirium is still not available and the MIND USA Study has shown that anti-psychotics are ineffective at treating delirium. This patient's presentation of "alert and calm with intermittent periods of agitation" is a common scenario, and initial therapy should focus on reorienting and getting the patient interactive and mobile (Answers A and D are incorrect; Answer C is correct). Dehydration is a common cause of agitation, and it should be addressed; however, with normal laboratory values and vital signs, this patient is unlikely dehydrated at this time (Answer B is incorrect).

6. **Answer: B**

In the general population, systemic corticosteroids are known to cause many neuropsychiatric events, including hyperactivity and agitation; in a recent study of adult ICU patients with acute lung injury, only age and use of systemic corticosteroids in the preceding 24 hours were independently associated with the transition to delirium from a non-delirious state (Answer B is correct). Benzodiazepines have a sedating effect and may calm an acutely agitated patient; however, they would not be recommended in this patient because they could worsen her confusion or delirium (Answer A is incorrect). The PADIS guidelines state that no evidence supports the use of haloperidol to reduce the duration of delirium (Answer C is incorrect). Vancomycin is not currently recognized as a cause of delirium; therefore, changing to linezolid is not indicated (Answer D is incorrect).

7. **Answer: D**

The midazolam dose is high, and the patient is "deeply sedated"; therefore, adding another benzodiazepine will likely not improve this patient's clinical status. Quetiapine has no indication for general sedation in a critically ill patient, and it should not be a consideration for sedation in this patient with severe ARDS. Dexmedetomidine is considered a weak sedative with no effect on respiratory drive; therefore, it would likely not improve this patient's ventilator dyssynchrony and hypoxia (Answers A–C are incorrect). At this stage in the patient's clinical course, it is reasonable to consider an NMDA. In a 2010 study of cisatracurium versus placebo for 48 hours in early ARDS, the cisatracurium group had more days free of mechanical ventilation and decreased mortality (30% vs. 44%) at 90 days for the subgroup of patients with severe ARDS ($\mathrm{Pa{\small O}_2/F{\small I}{\small O}_2}$ ratio less than 120 mm Hg). The incidence of pneumothorax was lower in the cisatracurium group than in the placebo group (4% vs. 11%). There were more days free of organ failure (non-lung) in the cisatracurium group than in the placebo group (15.8 vs. 12.2 days) in the first 28 days. A recent meta-analysis concluded that using short-term cisatracurium in patients with severe ARDS decreases mortality and time on mechanical ventilation compared with placebo. The risk of prolonged neuromuscular weakness was not found in these studies; however, use beyond 48 hours may increase this risk (Answer D is correct).

8. **Answer: C**

The TOF method of assessment is primarily used to help determine the degree of neuromuscular blockade and should not be used to titrate the dose of the NMBA. The patient's clinical status and laboratory values are the true determinants for dose adjustment of the NMBA. Patients may be at their clinical goal with a TOF of 2 or 3 twitches of 4. This is the ideal scenario, and it will predict a faster reversal of neuromuscular blockade (Answer C is correct). A TOF of 0 or 1 of 4 twitches predicts a significantly slower neuromuscular recovery time, and clinicians should try to decrease the NMBA as soon as the patient is clinically stable by laboratory values and ventilator management (Answer D is incorrect). A baseline electrical current intensity (amperage) should be established before the onset of neuromuscular blockade and should not be changed during paralysis unless a new baseline is indicated (Answer A is incorrect). As the electrical intensity (amperage) is established, an increase in the amperage is not indicated during infusion of the NMBA in order to increase the number of twitches. A decrease in the dose of NMBA would be indicated if an increase in the number of twitches were the clinical goal (Answer B is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: D**

Propofol infusion syndrome is a well-documented and complex set of adverse events, potentially resulting in multiorgan failure. An elevation in lactate, creatine kinase, transaminases, SCr, and triglycerides and the presence of a metabolic acidosis are some of the abnormalities that should concern the critical care provider for the presence of PRIS (Answer D is correct). Both DVT and critical illness polyneuropathy are serious concerns in the ICU patient; however, the abnormalities in the case are not representative of these complications (Answers A and B are incorrect). There are currently no known abnormal laboratory values to help determine whether delirium is present in an ICU patient (Answer C is incorrect).

2. **Answer: B**

This patient is at risk of propylene glycol toxicity after receiving a lorazepam drip for more than 48 hours. Lorazepam is dissolved in propylene glycol, an alcohol that can induce an osmolar gap and metabolic lactic acidosis, particularly in patients with significant hepatic or renal failure. Quantitative propylene glycol levels may be unavailable; therefore, surrogate markers such as an abnormal osmolar gap (greater than 10 mmol) and metabolic acidosis may indicate propylene glycol toxicity and a need to discontinue lorazepam. Although lorazepam drips are not routinely used for general sedation in adult ICUs, they may be used for other indications (e.g., severe EtOH [ethyl alcohol] or benzodiazepine withdrawal), and clinicians should remain aware of this serious complication (Answer B is correct). With an oxygen saturation of 98% on 2 L of oxygen, this patient does not meet the predefined criteria of ARDS (Answer A is incorrect). Encephalopathy will not cause a metabolic acidosis; therefore, an ammonia concentration would not be helpful at this stage (Answer C is incorrect). With a low fractional excretion of sodium and a high BUN/SCr ratio, the patient's laboratory values are indicative of a pre-renal concern versus acute tubular necrosis (Answer D is incorrect).

3. **Answer: D**

It is inappropriate to initiate an NMBA in a patient who has a sedation score indicating "agitation." This implies that the patient may potentially detect pain or discomfort while paralyzed (Answers B and C are incorrect). The goal should be to achieve a deeply sedated and/or non-agitated state before initiating an NMBA in an effort to avoid any patient discomfort that may be undetected during paralysis (Answer D is correct). The SAT would be inappropriate in someone who is rated "agitated" on the sedation scale or in a patient requiring escalating doses of sedation (Answer A is incorrect).

4. **Answer: B**

The pharmacokinetics/dynamics of prolonged fentanyl infusions have not been well described in the adult ICU population. Most data for fentanyl are derived from short-term infusions or boluses in healthy volunteers and in animal models. Fentanyl is hepatically metabolized primarily by the CYP3A4 enzyme, and decreased clearance of fentanyl has been described in patients with significant liver disease. Other properties of fentanyl (e.g., high volume of distribution, high protein binding, and high lipophilicity) may contribute to unpredictable clearance and a prolonged context-sensitive half-time for patients in acute renal failure or in patients who have inadequate nutritional status (Answer B is correct). Propofol is a CYP3A4 inhibitor; therefore, it should not induce the metabolism of fentanyl (Answer C is incorrect). Propofol is known to chelate trace elements and increase urinary loss of zinc when used for more than 5 days; propofol has not been shown to cause hypocalcemia (Answer D is incorrect). Disease states identified as risk factors for PRIS may include sepsis, acute liver failure, and history of pancreatitis; ARDS is not currently a documented risk factor (Answer A is incorrect).

5. **Answer: B**

Withdrawal from certain home medications may occur if these medications are not reinitiated within a few days of admission. The onset of withdrawal symptoms will vary depending on the half-life of each medication. Symptoms may include agitation, anxiety, psychosis, insomnia, hypertension, and tachycardia and can occur with medications such as opiates, GABA receptor agonists, antiepileptics, antidepressants, and antipsychotics. A pharmacist can assist the medical team by obtaining a thorough medication history and assessment of home medication compliance to help identify drug withdrawal symptoms. Reinitiating these medications can be considered unless contraindicated because of the clinical scenario (e.g., drug-drug interactions, drug-disease state interactions). The Agitation and Sedation section of the PADIS guidelines discusses identifying and treating the etiology of agitation before adding other medications; fentanyl should treat this patient's chronic pain and treat opiate/tramadol withdrawal (Answer B is correct). Adding quetiapine or lorazepam for agitation would not address or treat the underlying etiology of potential opiate/tramadol withdrawal (Answers A and C are incorrect). Patient-controlled analgesia with an opiate would help treat opiate withdrawal; however, this patient is not alert enough to use it (Answer D is incorrect).

6. **Answer: D**

Up to 30%–60% of ICU patients may go through alcohol withdrawal on cessation of alcohol use. The presence of alcohol withdrawal in ICU patients may prolong their ICU stay, increase hospital costs significantly, and lead to other complications during the hospital stay. Early and aggressive symptom-triggered management with a benzodiazepine, particularly in a patient with a history of alcohol withdrawal, is a key element in management. There is no otherwise published protocol for alcohol withdrawal in ICU patients. In this case, although dexmedetomidine is useful as an adjunctive agent to help decrease sympathetic storm and agitation secondary to alcohol withdrawal, it is not currently recommended for use as a single agent for alcohol withdrawal (Answer A is incorrect). Opiates do not treat alcohol withdrawal (Answer C is incorrect). Phenytoin is a known antiepileptic for use in epilepsy; however, it has not been shown to be effective in preventing or treating alcohol withdrawal (Answer B is incorrect). Benzodiazepines are the drugs of choice for alcohol withdrawal seizures; therefore, midazolam is the most appropriate drug for this patient, whose medical history is significant for recurrent alcohol withdrawal seizures (Answer D is correct).

7. **Answer: B**

This patient is at risk of delirium given the patient's age and being critically ill in the ICU. Avoiding medications that may cause or worsen delirium, such as benzodiazepines, is a strong recommendation in the PAD guidelines (Answer D is incorrect). With a QTc of 550 milliseconds, increasing the quetiapine dose for agitation could further increase the QTc and put this patient at high risk of cardiac arrhythmias. Starting quetiapine would not be the best option (Answer A is incorrect). Starting nonpharmacologic management of agitation/delirium is the best option (Answer B is correct). Dexmedetomidine does not prolong the QTc and should be continued in the setting of agitation (Answer C is incorrect).

8. **Answer: D**

Dementia is a progressive and chronic state of cognitive impairment that worsens over weeks to months; this differs from the acute onset characteristic of ICU delirium (Answer A is incorrect). Alcohol withdrawal should always be a consideration for patients who become altered or agitated in the ICU. This patient's vital signs are normal, and she is presenting in a hypoactive state; these findings are not typical for acute alcohol withdrawal, and alternative causes for her decline in mental status need to be considered (Answer B is incorrect). Adrenal insufficiency in the ICU usually presents with abnormal laboratory values and/or hemodynamic instability. This patient's laboratory values and hemodynamics are reported as normal; therefore, adrenal insufficiency is unlikely (Answer C is incorrect). Both iatrogenic and non-iatrogenic causes for delirium are well documented in the literature. Dehydration and infection are common causes of delirium, particularly in the older adult population. This patient has several reasons for being dehydrated in the hospital: NPO status, persistent fevers, and taking hydrochlorothiazide. Untreated infection or lack of source control is also a concern with the presence of persistent fever, even while the patient is taking antibiotics (Answer D is correct).

Pulmonary Disorders I

Grace E. Benanti, Pharm.D., BCCCP

Loyola University Medical Center
Maywood, Illinois

PULMONARY DISORDERS I

GRACE E. BENANTI, PHARM.D., BCCCP

LOYOLA UNIVERSITY MEDICAL CENTER
MAYWOOD, ILLINOIS

Learning Objectives

1. Recommend an evidence-based therapeutic plan to manage critically ill patients with acute respiratory distress syndrome.
2. Assess appropriateness of drug therapy for endotracheal intubation, including agents for premedication, induction, and neuromuscular blockade.
3. Evaluate key variables and commonly used modes for treatment with mechanical ventilation.

Abbreviations in This Chapter

AC/VC	Assist control/volume control
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease 2019
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
MAP	Mean arterial pressure
MV	Mechanical ventilation
NMBA	Neuromuscular blocking agent
PEEP	Positive end-expiratory pressure
PS	Pressure support
RSI	Rapid sequence intubation
SIMV	Synchronized intermittent mandatory ventilation

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Which best describes the category of acute respiratory distress syndrome (ARDS) that most benefits from prone positioning and cisatracurium administration?

   A. Acute lung injury.
   B. Moderate to severe.
   C. Mild to moderate.
   D. Mild.

2. Several clinical trials have been conducted in moderate to severe ARDS. Which of the following partial pressure of arterial oxygen (Pa_{O_2})/ fraction of inspired oxygen (F_{IO_2}) parameters best describes this ARDS subpopulation?

   A. 100–200 mm Hg.
   B. Greater than 150 mm Hg.
   C. Less than 150 mm Hg.
   D. 50–150 mm Hg.

3. Which of the following parameters best describes "low tidal volumes" for invasive mechanical ventilation in ARDS?

   A. 6 mL/kg of total body weight.
   B. 4 mL/kg of ideal body weight.
   C. 7 mL/kg of total body weight.
   D. 5 mL/kg of adjusted body weight.

4. A 65-year-old man presents to the emergency department with severe shortness of breath, tachypnea, altered mental status, and diaphoresis. A chest radiograph reveals diffuse, bilateral opacities. His vital signs are as follows: blood pressure 94/54 mm Hg, respiratory rate 26 breaths/minute, heart rate 120 beats/minute, pain score 2/10, and temperature 105.8°F (41.0°C). The patient's wife states that his symptoms began about 2 days ago and gradually worsened over the past day. The patient is transferred to the ICU, where he is intubated. His arterial blood gas values are pH 7.30, partial pressure of arterial carbon dioxide (Pa_{CO_2}) 50 mm Hg, Pa_{O_2} 50 mm Hg, and oxygen saturation (Sa_{O_2}) 85% while receiving F_{IO_2} 100%. Which is the best therapy plan for the next 24 hours?

   A. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a Richmond Agitation-Sedation Scale (RASS) score of −4; and prone positioning.
   B. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of −5 and cisatracurium administration to limit plateau pressures; and prone positioning.

C. Empiric antibiotic therapy, aggressive diuresis (goal central venous pressure less than 4 mm Hg), and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of –4; and prone positioning.
D. Empiric antibiotic therapy, intravenous fluid resuscitation, and vasopressors for shock; low tidal volume (4–8 mL/kg) ventilation strategy; deep sedation to achieve a RASS score of –4; and supine positioning.

5. P.D. is a 67-year-old woman (height 160 cm; total body weight 68 kg) admitted to the ICU with ARDS pneumonia. Her mechanical ventilation parameters are as follows: tidal volume 280 mL, respiratory rate 20 breaths/minute, positive end-expiratory pressure (PEEP) 12 cm H_2O, and F_{IO_2} 80% with plateau pressure of 22 mm Hg. Her mean arterial pressure (MAP) is currently 68 mm Hg with norepinephrine discontinued 4 hours ago and CVP ranging between 8 and 14 cm H_2O over the last 2 hours. Also, her total urine output over the past 24 hours is 1150 mL. The ICU team is discussing fluid management using the FACTT Lite protocol. Which of the following options is the most appropriate strategy?

A. Administer furosemide 40 mg IV once and re-evaluate in 4 hours.
B. Administer furosemide 1 mg/h continuous infusion and re-evaluate in 8 hours.
C. Administer 0.9% sodium chloride 500 mL over 1 hour and re-evaluate in 4 hours.
D. Monitor only and re-evaluate in 8 hours.

6. Which of the following statements most appropriately describes published clinical trials of corticosteroids in ARDS?

A. Dexamethasone demonstrated improved clinical outcomes among ARDS patients on lung-protective strategies.
B. Dexamethasone initiated 7 days after ARDS onset was associated with worse clinical outcomes.
C. Methylprednisolone demonstrated improved clinical outcomes among ARDS patients on lung-protective strategies.
D. Methylprednisolone initiated 7 days after ARDS onset was associated with worse clinical outcomes.

7. Which order of medication administration would be most appropriate for a 34-year-old woman with no significant medical history receiving rapid sequence intubation (RSI)?

A. Rocuronium, etomidate, midazolam.
B. Fentanyl, succinylcholine, propofol.
C. Atropine, rocuronium, etomidate.
D. Fentanyl, etomidate, succinylcholine.

8. A 78-year-old man (weight 70 kg) presents to the ICU after being intubated for acute respiratory failure. His ventilator settings are as follows: assist control/volume control mode, tidal volume 700 mL (10 mL/kg), respiratory rate 20 breaths/minute, F_{IO_2} 50%, PEEP 5 cm H_2O, and pressure support 10 cm H_2O. The first arterial blood gas values are pH 7.25, Pa_{CO_2} 65 mm Hg, HCO_3 26 mEq/L, Pa_{O_2} 65 mm Hg, and Sa_{O_2} 90%. His MAP is 72 mm Hg without requiring vasoactive support, with a serum creatinine of 1.2 mg/dL and urinary output of 350 mL over the past 6 hours. Which approach would be best for this patient's initial treatment?

A. High tidal volume mechanical ventilation (MV) and conservative fluid management.
B. Low tidal volume MV and conservative fluid management.
C. High tidal volume MV and liberal fluid management.
D. Low tidal volume MV and liberal fluid management.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 2, 6
    b. Task B: 2, 3
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1, 3, 6, 7
    b. Task B: 1, 13
    b. Task C: 1
3. Domain 3: Personal Practice
    a. Task B: 1

I. ACUTE RESPIRATORY DISTRESS SYNDROME

A. Definition and Epidemiology
  1. First described in 1967; several definitions have evolved over the years
  2. The Berlin ARDS definition was established in 2012 to address issues with previous definitions (Table 1) (JAMA 2012;307:2526-33).

Table 1. Berlin ARDS Definition

Variable	Criteria
Timing	Onset within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (ie, ECHO) to exclude hydrostatic edema if no risk factors present
Oxygenation	
Mild	200 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Moderate	100 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe	Pa_{O_2}/F_{IO_2} ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O

ARDS = acute respiratory distress syndrome; CPAP = continuous positive airway pressure; ECHO = echocardiogram; F_{IO_2} = fraction of inspired oxygen; Pa_{O_2} = partial pressure of oxygen; PEEP = positive end-expiratory pressure..

  3. In 2014, ARDS represented 10.4% of all ICU admissions and 23.4% of patients requiring mechanical ventilation (MV) (JAMA 2016;315:788-800).
    a. Of these, mild ARDS accounted for 30%, moderate for 46.6%, and severe for 23.4%.
    b. Hospital mortality was 34.9% for mild ARDS, 40.3% for moderate ARDS, and 46.1% for severe ARDS.
    c. During the COVID-19 pandemic, ARDS occurred at a rate of 50% to 80% compared with the general ICU population (BMJ. 2024;369:e076612).
    d. Multisystem organ failure is the leading cause of death in patients with ARDS, with the number of extrapulmonary organ failures correlating with an incremental increase in mortality (Intensive Care Med 2011;37:1932-41).

B. Causes and Pathophysiology
  1. Direct and indirect causes of lung injury
    a. Direct: Pneumonia, aspiration, trauma
    b. Indirect: Sepsis, transfusion injury, pancreatitis, burn injury, trauma
  2. Pathogenesis
    a. The hallmark clinical manifestation of ARDS is hypoxemia from alveolar collapse and edema.
    b. The exudative phase is characterized by increased permeability from the alveolar epithelium and capillary endothelial complex damage, leading to diffuse alveolar edema with fluid and cellular debris (e.g., neutrophils, cytokines, platelets). In addition, type II cells responsible for surfactant production are damaged. The peak incidence of this phase typically occurs within the first week after the initial insult.
    c. The fibroproliferative phase marks either recovery or progression of ARDS. Patients may partly or fully recover pulmonary function from drainage of the alveolar fluid, type II cellular repair, and improvement in the integrity of the endothelium-epithelium complex. However, patients whose conditions are progressively worsening may develop significant alveolar, interstitial, and capillary fibrosis. This phase typically manifests later in the course of ARDS (i.e., more than 7 days after the initial insult).

C. Management Strategies
  1. MV
     a. Lung-protective strategies using low tidal volume ventilation are considered the standard of care and cornerstone in managing ARDS.
     b. The landmark multicenter trial by the Acute Respiratory Distress Syndrome Network (ARDSNet) showed a survival benefit over conventional ventilation using higher tidal volumes (12 mL/kg) (N Engl J Med 2000;342:1301-8). Clinical practice guidelines recommend limiting tidal volumes (4–8 mL/kg of predicted body weight) (Am J Respir Crit Care Med 2017;195:1253-63; Intensive Care Med 2023;49:727-759) and inspiratory pressures (plateau pressure less than 30 cm H_2O) (Am Respir Crit Care Med 2017;195:1253-63). Although optimizing higher PEEP values may be beneficial (Am J Respir Crit Care Med 2017;195:1253-63), individualizing PEEP in ARDS remains unclear (Intensive Care Med 2023;49:727-59). Although predicted body weight and ideal body weight are not identical, clinicians often apply ideal body weight for tidal volumes for ease of use and familiarity.
  2. Prone positioning
     a. Prone over supine positioning improves gas exchange and may reduce ventilator-induced lung injury. Compression atelectasis attributed to the weight of the heart, ventral lungs, and abdominal viscera may be exacerbated in the supine position in patients with ARDS. The gravitational effects by placing a patient in the prone position improve ventilation/perfusion matching and end-expiratory lung volume by more homogeneous tidal volume delivery (Chest 2017;151:215-24; Am J Respir Crit Care Med 2017;195:1253-63).
     b. The PROSEVA study group represents the most recently published randomized clinical trial comparing prone and supine positioning in ARDS. In this trial, prone positioning for at least 16 hours/day compared with supine positioning in early ARDS decreased 28-day (adjusted hazard ratio [HR] 0.42; 95% confidence interval [CI], 0.26–0.66) and 90-day (adjusted HR 0.48; 95% CI, 0.32–0.72) mortality (N Engl J Med 2013;368:2159-68). Significantly more ventilator-free days at days 28 and 90 were observed with proning. Furthermore, 90-day extubation rates were significantly higher in patients in the prone position.
     c. Several meta-analyses have suggested an overall mortality benefit associated with prone positioning over supine in ARDS, though this finding was inconsistent (Intensive Care Med 2014;40:332-41; Crit Care 2014;18:R109; Crit Care Med 2014;42:1252-62; Ann Am Thorac Soc 2017;14(suppl 4):S280-S8; J Thorac Dis 2015;7:356-67; Am J Respir Crit Care Med 2021;203:1366-77). However, most meta-analyses have shown a survival benefit with proning in patients with moderate to severe ARDS (i.e., PaO_2/FIO_2 less than 150 mm Hg) compared with mild hypoxemia (i.e., PaO_2/FIO_2 greater than 200 mm Hg) (Crit Care 2014;18:R109; Crit Care Med 2014;42:1252-62; Ann Am Thorac Soc 2017;14(suppl 4):(S280-S8). Similarly, mortality was reduced in patients with ARDS with prone positioning and concurrent lung-protective MV strategies compared with pronation and high tidal volume ventilation (Intensive Care Med 2014;40:332-41; Crit Care Med 2014;42:1252-62; J Thorac Dis 2015;7:356-67; Am J Respir Crit Care Med 2021;203:1366-77). Prone positioning in moderate and severe ARDS has been associated with the greatest reduction in mortality compared with other strategies, including ECMO (Am J Respir Crit Care Med 2021;203:1366-77).
     d. Implementation of prone positioning requires robust planning and resources (J Pharm Pract 2019;32:347-60). Contraindicated criteria of use should be established to mitigate any adverse events (e.g., spinal cord injury, elevated intracranial pressure [ICP]). Health care providers should be trained on appropriate movement of patients between supine and prone positioning to ensure securing of central lines as well as the endotracheal tube. Institutions should also consider the need for manual maneuvering of patients compared with specialized rotating beds. One important patient safety consideration is rapid health care staff access to patients in specialized beds during medical emergencies (e.g., cardiopulmonary arrest, self-extubation).

e. Recently published clinical practice guidelines strongly recommend prone positioning in moderate to severe ARDS (Table 2) (Am J Respir Crit Care Med 2017;195:1253-63; BMJ Open Respir Res 2019;6:e000420; Ann Intensive Care 2019;9:69; Intensive Care Med 2023;49:727-59). Despite the overwhelming support for this therapy in ARDS, several important questions remain, including the optimal duration and timing of use pertaining to ARDS onset. Patients with ARDS should remain in the prone position for more than 12 hours each day, with consideration for longer daily durations (i.e., at least 16 hours per day). Prone positioning therapy should be considered early in the course of ICU admission in patients with moderate to severe ARDS.

Table 2. Clinical Practice Guideline Recommendations for Prone Positioning in ARDS

Source	Summary	GRADE Recommendation
Am J Respir Crit Care Med 2017;195:1253-63	Suggest prone positioning > 12 hr/day	Strong recommendation; moderate-high level of evidence
BMJ Open Respir Res 2019;6:e000420	• NOT recommended for all levels of ARDS severity • Recommended for at least 12 hr/day in moderate to severe ARDS (i.e., PaO_2/FIO_2 < 150 mm Hg)	Strongly in favor
Ann Intensive Care 2019;9:69	Should be used in moderate to severe ARDS (PaO_2/FIO_2 < 150 mm Hg) for at least 16 consecutive hr	High level of evidence
Intensive Care Med 2023;49:727-59	Recommend using early after intubation in moderate to severe ARDS (PaO_2/FIO_2 < 150 mm Hg for at least 16 consecutive hours)	Strong recommendation; high level of evidence

3. Extracorporeal membrane oxygenation (ECMO)
   a. The CESAR trial showed that treatment at an ECMO referral center improved 6-month survival (Lancet 2009;374:1351-63).
      i. ARDS with a Murray score (i.e., acute lung injury score on the basis of chest radiography, hypoxemia score, peak end-expiratory pressure, and static compliance) of 3 or greater, or hypercapnia and a pH less than 7.20
      ii. Not all patients randomized to the ECMO referral center received ECMO (around 24% of patients in the experimental group did not receive ECMO).
      iii. Potential for confounding because of experiential bias – Clinicians at an ECMO treatment center may have more experience in treating ARDS.
   b. The Respiratory ECMO Survival Prediction (RESP) score was developed from a registry of patients receiving ECMO (Am J Respir Crit Care Med 2014;189:1374-82).
      i. The RESP score predicts patient survival after ECMO initiation.
      ii. Does not help quantify the decision to initiate ECMO or determine if ECMO treatment will improve survival in a specific patient
   c. In the EOLIA trial, early use of ECMO compared with conventional management in severe ARDS (e.g., PaO_2/FIO_2 less than 80 mm Hg) was not associated with reduced 60-day mortality rates (relative risk [RR] 0.76; 95% CI, 0.55–1.04, p=0.09) (N Engl J Med 2018;378:1965-75).
      i. This trial was prematurely discontinued because of predefined futility criteria, which resulted in not achieving power.
      ii. Furthermore, bias was attributed to the high crossover rate of 28% of controls into the ECMO group.

   d. The 2019 clinical practice guidelines state that ECMO should be considered in patients with severe ARDS or more specifically with PaO_2/FIO_2 ratios less than 80 mm Hg and/or in patients with elevated plateau pressures despite optimizing PEEP, neuromuscular blocking agents (NMBAs), and prone positioning (BMJ Open Respir Res 2019;6:e000420; Ann Intensive Care 2019;9:69). The 2023 ESICM clinical practice guidelines recommend ECMO use in severe ARDS (as defined in EOLIA trial eligibility criteria) at an established ECMO center (strong recommendation; moderate level of evidence in favor) (Intensive Care Med 2023;49:727-59). The 2024 American Thoracic Society (ATS) guidelines suggest the use of veno-venous ECMO (VV ECMO) in patients early in their course (less than 7 days) with reversible etiologies of respiratory failure and very severe hypoxemia ($PaCO_2/FIO_2$ ratio less than 80 mm Hg) or hypercapnia (pH less than 7.25 with $PaCO_2$ 60 mm Hg) after optimizing conventional treatments (*Am J Respir Crit Care Med.* 2024;209(1):24-36).
   e. Concomitant VV ECMO and prone positioning
      i. A meta-analysis (n=13 studies including only 1 randomized clinical trial) evaluated the clinical impact of prone positioning and VV ECMO in ARDS compared with VV ECMO alone (Intensive Care Med 2022;48:270-80).
      ii. Pooled data showed combination VV ECMO and prone positioning 28-day survival was significantly improved (n=10 studies; RR 1.31; 95% CI, 1.21–1.41). Also, combination therapy was also associated with significantly improved ICU and in-hospital survival as well as overall 60- and 90-day survival.
      iii. A priori subgroup analyses found improved 28-day survival with concomitant prone positioning and VV ECMO in both patient cohorts with COVID-19 ARDS patients (n=6 studies; RR 1.32; 95% CI, 1.15–1.50) and ARDS patients without COVID-19 (n=4 studies; RR 1.30; 95% CI, 1.19–1.43).
      iv. Pooled data also showed significant improvements in ventilator-free days at day 28 (n=9 studies; RR −1.29; 95% CI, −2.39 to −0.19) with prone positioning and VV ECMO over ECMO alone in ARDS patients
      v. No major complications were reported with either study group.

4. Fluid management
   a. The FACTT trial compared 2 optimal fluid management strategies (conservative (CVP less than 4 mm Hg) and liberal (CVP 10–14 mm Hg) in patients with ARDS and hemodynamic stability (not requiring vasopressors or MAP greater than 60 mm Hg) (N Engl J Med 2006;354:2564-75). Diuretics were withheld in patients with shock but were administered according to study protocol once patients had established hemodynamic stability (discontinuation of vasopressors or MAP greater than 60 mm Hg). Although 60-day mortality did not differ (p=0.30), the conservative compared with the liberal strategy was associated with increased ventilator-free days (14.6 ± 0.5 vs. 12.1 ± 0.5, p<0.001) and ICU-free days (28 days) (13.4 ± 0.4 vs. 11.2 ± 0.4, p<0.001).
   b. Fluid strategies were compared (conservative, liberal, and simplified conservative) in a retrospective comparison among protocols pertaining to ARDS (Crit Care Med 2015;43:288-295). The FACTT Lite protocol provides fluid management recommendations pertaining to the administration of furosemide or fluids as well as monitoring without intervention-based CVP, MAP, urinary output, and pulmonary artery occlusion pressure (optional) (Table 3). No significant differences were found between the FACTT Lite and the FACTT conservative strategies for ventilator-free days (14.9 vs. 14.6, respectively; p=0.61), ICU-free days (14.4 vs. 13.4, respectively; p=0.054), or death at 60 days (22% vs. 25%, respectively; p=0.15). Conversely, the FACTT Lite approach had improved outcomes (ventilator-free, ICU-days, and 60-day mortality) compared with the FACTT liberal approach.
   c. A meta-analysis evaluated the safety and efficacy of conservative versus liberal fluid strategies in ICU patients with either ARDS or sepsis (Intensive Care Med 2017;43:155-70). No differences in mortality were found between study groups in the ARDS subgroup (n=5 studies; RR 0.91; 95% CI, 0.77–1.07) or the mixed ARDS and sepsis subgroup (n=2 studies; RR 0.95; 95% CI, 0.80–1.14).

Table 3. FACTT Lite Simplified Conservative Fluid Management Approach[a]

CVP (Recommended)	Pulmonary Artery Occlusion Pressure (optional)	MAP ≥ 60 mm Hg AND No Vasoactive Support ≥ 12 Hr	
		Urinary Output < 0.5 mL/kg/hr	**Urinary Output ≥ 0.5 mL/kg/hr**
> 8	> 12	Administer furosemide and reevaluate in 1 hr	Administer furosemide and reevaluate in 4 hr
4–8	8–12	Administer fluid bolus and reevaluate in 1 hr	Administer furosemide and reevaluate in 4 hr
< 4	< 8	Administer fluid bolus and reevaluate in 1 hr	Monitor and reevaluate in 4 hr

[a] Initial recommended furosemide dosing = 20-mg bolus or 3-mg/hr infusion. Recommended 2-fold incremental increase in subsequent furosemide doses up to a maximum of 160-mg bolus/24-mg/hr infusion rate or until goal CVP/pulmonary artery occlusion pressure achieved. See clinical trial publication for further details.
CVP = central venous pressure; MAP = mean arterial pressure.

   d. The RADAR-2 trial also evaluated the conservative and standard of care fluid strategies in critically ill patients (n=180) (Intensive Care Med 2022;48:190-200). Although this randomized clinical trial was not exclusively conducted in ARDS patients, subgroup analysis in ARDS was planned a priori. In the ARDS subgroup, no differences in mortality, mechanical ventilation duration, or ICU length of stay were observed between treatment arms. However, it must be noted that the sample size of ARDS patients in the intervention (n=19) and standard of care (n=11) study groups was very small, which may limit clinical interpretation for this patient population.

5. NMBAs
   a. Although the 2023 European Society of Intensive Care Medicine (ESICM) guidelines recommend against routine use of NMBAs, the 2024 ATS guidelines do recommend NMBAs in severe ARDS (P/F ratio less than 100 mm Hg) within 48 hours of ARDS onset with no recommendation for later initiation or less severe ARDS (*Am J Respir Crit Care Med.* 2024;209(1):24-36).
   b. Early administration (within 48 hours of ARDS onset) of cisatracurium over 48 hours has consistently improved oxygenation without increasing the risk of neuromuscular weakness.
   c. The ACURASYS trial showed decreased 90-day adjusted mortality with cisatracurium compared with placebo (HR 0.68; 95% CI, 0.48–0.98; p=0.04). Subgroup analysis suggested the greatest mortality benefit in patients with ARDS having a PaO_2/FIO_2 less than 120 mm Hg. Cisatracurium was also associated with significantly more ventilator-free days (up to 28 and 90 days) and organ failure–free days (up to 28 days). Cisatracurium did not significantly increase the risk of ICU-acquired neuromuscular weakness (N Engl J Med 2010;363:1107-16; Crit Care Med 2017;45:446-53).
   d. The ROSE trial showed no significant differences in 90-day mortality between cisatracurium (42.5%) and placebo (42.8%) (between-group difference -0.3 percentage points; 95% CI, -6.4 to 5.9; p=0.93). No differences between study groups were found for secondary end points at day 28, including in-hospital mortality, days free of MV, and days not in the ICU or hospital (N Engl J Med 2019;380:1997-2008).
   e. The optimal strategy for NMBA dosing and monitoring in ARDS remains debatable. The ACURASYS and ROSE trials had similar dosing strategies of a cisatracurium 15-mg bolus followed by continuous infusion at 37.5 mg/hour over 48 hours without titration or train-of-four monitoring. Additional boluses were allowed in patients with elevated plateau pressures (i.e., greater than 30 cm H_2O), given concerns for increased risk of ventilator-induced lung injury. However, differing sedation practices with non-paralyzed patients and lack of proning in the ROSE trial may account for the differing results.
   f. The ESICM 2023 clinical practice guidelines recommend against routine use of NMBAs in ARDS (strong recommendation, moderate level of evidence) (Intensive Care Med 2023;49:727-59).

6. Corticosteroids
   a. Proposed rationale for corticosteroid use in ARDS was to prevent fibroproliferation with subsequent alveolar fibrosis from a proinflammatory response.
   b. Steroids may improve oxygenation, but randomized trials found no definitive mortality benefit. Although the optimal timing of use remains unknown, consideration may be given in patients with early (less than 7 days) and late (7 days or more), whereas initiation beyond 14 days after onset was associated with higher death rates in the LaSRS trial. (N Engl J Med 2006;354:1671-84; JAMA 1998;280:159-65; Crit Care Med 2017;45:2078-88). However, the increased death risk in patients initiated on steroids after 14 days of ARDS onset may be misleading. It should be noted this specific cohort had significant baseline characteristic variation or difference as well as atypically low death rates in the control group for 60-day (8%) and 180-day (12%) mortality (N Engl J Med 2006;354:1671-84). Furthermore, no significant differences in mortality were found between steroid and control groups in the greater than 14 days cohort after adjusting for important baseline covariates (Crit Care 2007;11:425). The 2024 Society of Critical Care Medicine (SCCM) Focused Update: Guidelines on Use of Corticosteroids updated their recommendations from 2017, removing the specification of "early moderate to severe ARDS." Both the SCCM and the 2024 ATS ARDS guidelines suggest the use of corticosteroids and provide no specific recommendation to choose between steroid molecules.
   c. The DEXA-ARDS clinical trial was the first randomized, placebo-controlled clinical trial investigating dexamethasone for patients with early moderate to severe ARDS (Lancet Respir Med 2020;8:267-76). The corticosteroid group consisted of dexamethasone 20 mg intravenously daily over the first 5 days, followed by 10 mg intravenously daily for up to 10 days or upon extubation (if occurring prior to day 10). Dexamethasone was associated with increased mean ventilator-free days over placebo at 1 month (12.3 ± 9.9 and 7.5 ± 9.9 days, respectively; $p<0.0001$). Other secondary outcomes, including mortality (all-cause, ICU, in-hospital) and MV duration (among all ICU survivors at day 60), significantly favored the dexamethasone group. Of note, hyperglycemia, secondary infections, and barotrauma were similar between study groups. The novelty of this trial compared with previously published corticosteroid studies was the concurrent use of contemporary lung-protective MV strategies.
   d. Published guidelines provide minimal direction for clinical practice decision-making regarding the best approach for corticosteroid use in ARDS (*BMJ Open Respir Res*. 2019;6:e000420; *Ann Intensive Care*. 2019;9:69; *Crit Care Med*. 2017;45:2078-8888). The 2017 guidelines suggest use in selected patients with ARDS, whereas neither of the 2019 guidelines provides any recommendations because of the paucity of quality data (Table 4).

Table 4. Clinical Practice Guideline Recommendations for Corticosteroids in ARDS

Source	Summary	GRADE Recommendation
Annane 2017	Suggest use in early moderate to severe ARDS ($Pa_{O_2}/F_{IO_2} < 200$ mm Hg AND within 14 d of onset)	Conditional recommendation; moderate quality of evidence
Griffiths 2019	Limited quality data, resulting in inability to make a recommendation; rather, states that further research is warranted	Research recommendation
Papazian 2019	Not reported	Not reported
Crit Care Med. 2024;52(5):e219-e233 2024	Suggest use in adult critically ill patients with ARDS	Conditional recommendation; moderate quality of evidence
Qadir 2024	Suggest use in patients with ARDS	Conditional recommendation; moderate quality of evidence

Abbreviations: ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen.

Table 5. Clinical Practice Guideline Recommendations for Corticosteroids in Critically Ill Patients with COVID-19

Source	Summary	GRADE Recommendation
www.covid19treatmentguidelines.nih.gov Last updated February 29, 2024	Recommends dexamethasone for most patients requiring mechanical ventilation or ECMO	Strong recommendation
www.idsociety.org/COVID19guidelines Last updated September 25, 2020	Recommends dexamethasone rather than no dexamethasone	Strong recommendation, moderate certainty of evidence
Crit Care Med 2021;49:e219-234	• Recommends using a short course of systemic corticosteroids over not using corticosteroids • Suggests specifically using dexamethasone over other corticosteroid derivatives	• Strong recommendation, moderate level of evidence • Weak recommendation, very low level of evidence

7. Corticosteroids in COVID-19 (see the Infectious Diseases I chapter for further information)
   a. Currently, clinical practice guidelines strongly recommend the use of dexamethasone in ICU patients with COVID-19 (Table 5).
   b. The landmark RECOVERY clinical trial compared dexamethasone 6 mg daily up to 10 days total administered either orally or intravenously compared to usual care alone in 6425 hospitalized patients with COVID-19 (N Engl J Med 2021;384:693-704). Among 1007 patients in the prespecified subgroup analysis requiring invasive MV, the 28-day mortality rate was significantly lower in the dexamethasone group (29.3%) than in the usual care group (41.4%) (RR 0.64; 95% CI, 0.51–0.81). In addition, the probability of hospital discharge within 28 days among those receiving invasive MV significantly improved in patients receiving dexamethasone over usual care (RR 1.45; 95% CI, 1.13–1.85). Moreover, MV cessation was more likely with dexamethasone than with usual care (RR 1.47; 95% CI, 1.20–1.78). Similarly, use of dexamethasone lowered overall mortality among all hospitalized patients compared with usual care. However, a survival benefit was only observed among patients with COVID-19 requiring oxygen support (both invasive and noninvasive) over those without any respiratory support.
   c. The CoDEX clinical trial randomized 299 adult patients with COVID-19 with moderate to severe ARDS to either dexamethasone (20 mg intravenously daily over 5 days followed by 10 mg intravenously daily for another 5 days or until ICU discharge) or usual care (JAMA 2020;6;324:1307-16). The primary end point was ventilator-free days during the initial 28 days consisting of the number of days alive and liberation from MV for 48 hours or more. The mean number of ventilator-free days in the dexamethasone and usual care groups was 6.6 days and 4.0 days (adjusted difference of 2.26 days; 95% CI, 0.2–4.38; p=0.04), respectively. No differences were observed between study groups for secondary aims, including 28-day mortality, ICU-free days, overall MV days, or risk of adverse events. A limitation of this trial is that it was terminated early because of the publication of the RECOVERY trial findings. This may have introduced bias despite showing a positive benefit associated with dexamethasone.

- d. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group conducted a meta-analysis of seven randomized clinical trials involving 1703 critically ill patients with COVID-19. It should be noted most patients included in pooled analysis did not meet a strict definition of ARDS but were considered critically ill. This meta-analysis evaluated the impact of systemic corticosteroids, including dexamethasone, methylprednisolone, or hydrocortisone, on 28-day mortality (JAMA 2020;324:1330-41). Overall pooled data among all trials showed that systemic corticosteroids significantly reduced the risk of all-cause mortality (summary OR 0.66; 95% CI, 0.53–0.82; $p<0.001$) using a fixed-effects model. However, no association was observed between corticosteroids and controls using a random-effects meta-analysis approach (OR 0.70; 95% CI, 0.48–1.01). Subgroup analysis showed the survival benefit favored dexamethasone over no steroids according to pooled data from three clinical trials. Of note, this benefit with dexamethasone was largely driven by the RECOVERY trial consisting of 57% of the overall pooled data. The remaining clinical trials consisting of hydrocortisone (n=3) and methylprednisolone (n=1) showed that these agents did not affect survival according to subgroup analysis. In addition, no increased risk of adverse events was found between corticosteroid and control groups.
- e. The optimal dexamethasone dosing strategy remains unknown, though most clinicians have adopted the 6-mg/day approach used in the RECOVERY trial. In other words, higher dexamethasone dosing strategies (20 mg/day) have not shown additional beneficial effects compared with lower doses (6 mg daily) (JAMA 2020;324:1330-41).

8. Inhaled pulmonary vasodilators
    - a. Inhaled nitric oxide and inhaled epoprostenol have improved gas exchange, despite their lack of effect on clinical outcomes (length of stay and mortality). Limited data suggest these agents are equally efficacious. A meta-analysis of randomized clinical trials comparing inhaled nitric oxide and placebo showed no effect on mortality in patients with ARDS (RR 1.10; 95% CI, 0.94–1.29), patients with a baseline PaO_2/ FIO_2 of 100 mm Hg or less (RR 1.01; 95% CI, 0.78–1.32), or patients with a baseline PaO_2/FIO_2 greater than 100 mm Hg (RR 0.89; 95% CI, 0.89–1.42) (Crit Care Med 2014;42:404-12).
    - b. Institutions have used inhaled epoprostenol as a more cost-effective option over inhaled nitric oxide. Direct comparisons between these studies suggest safety and efficacy were similar. However, inhaled epoprostenol has been associated with significant cost savings over inhaled nitric oxide. Major limitations of widespread inhaled nitric oxide use for ARDS include high costs and dedicated equipment for drug delivery. Given that cost is the primary differentiating factor between these two agents, many institutions have transitioned from inhaled nitric oxide to inhaled epoprostenol. Implementation of inhaled epoprostenol delivery systems and processes requires continuous education and pharmacovigilance to mitigate the risk of medication errors and preventable adverse drug events.
    - c. The 2023 ESICM guideline and the 2024 ATS guideline did not evaluate inhaled epoprostenol; thus, they do not provide any recommendations on its use in ARDS. However, one of the 2019 guidelines states to avoid inhaled epoprostenol in ARDS because of weak quality of evidence (BMJ Open Respir Res 2019;6:e000420), whereas another provides an expert opinion statement for consideration in severe ARDS for patients currently receiving lung-protective ventilation and proning, but before ECMO (Ann Intensive Care 2019;9:69).

d. Despite the paucity of data for inhaled epoprostenol, it is commonly used in the ICU for ARDS as a bridge to more invasive management strategies (i.e., ECMO) and/or as salvage therapy. Although the optimal dosing regimen remains unknown, the most commonly used doses include a weight-based strategy (typically 10–50 ng/kg/minute titrated to effect) (J Pharm Pract 2019;32:347-60). A small prospective study evaluated a dose-response relationship of weight-based inhaled epoprostenol in patients with ARDS, titrating from 0 to 50 ng/kg/minute by increments of 10 ng/kg/minute every 30 minutes (Chest 2000;117:819-27). A significant increase in the absolute median Pa_{O_2}/F_{IO_2} was observed with the 50 ng/kg/minute weight-based dose compared with baseline (202.2 vs. 187.2 mm Hg, respectively; $p<0.008$). However, no significant difference was observed with the median Pa_{O_2}/F_{IO_2} (183.2 mm Hg) associated with the 10 ng/kg/minute regimen compared with baseline. Furthermore, no statistically significant difference was found between the 10 and 50 ng/kg/minute weight-based regimens regarding oxygenation indices. A major caveat of this study was small sample size (n=9), and the patient population was not reflective of contemporary clinical use of inhaled epoprostenol in moderate to severe ARDS, given that only three patients had a baseline Pa_{O_2}/F_{IO_2} less than 150 mm Hg. Recently, one study observed a similar effect on oxygenation using fixed-dose inhaled epoprostenol without titration compared with inhaled nitric oxide (J Intensive Care Med 2021;36:466-76).

e. One study directly compared weight-based and fixed-dose inhaled epoprostenol in ARDS patients (n=294) (Am J Health System Pharm 2023;80:S11-22). The mean Pa_{O_2}/F_{IO_2} increase from baseline to 4 hours after inhaled epoprostenol initiation was significantly higher in the the fixed-dose group compared with the weight-based dosing approach (81.1 ± 106.0 vs. 41.0 ± 72.5 mm Hg, respectively; p=0.0015). Also, responder rates at 4 hours after inhaled epoprostenol initiation was significantly higher with fixed-dosing over weight-based dosing (69.9% vs. 30.1%; p=0.02). Clinical outcomes were comparable between the two dosing groups.

Patient Cases

1. A 56-year-old man is admitted to the ICU with ARDS after experiencing increasing dyspnea during the past 24 hours. His medical history is significant for alcoholism and hypertension. Results of the initial arterial blood gas are as follows: pH 7.24, Pa_{CO_2} 58 mm Hg, HCO_3 24 mEq/L, Pa_{O_2} 50 mm Hg, and Sa_{O_2} 84% while receiving MV AC mode with F_{IO_2} 100%. Chest radiography reveals diffuse bilateral infiltrates. The patient has blood pressure 120/40 mm Hg (MAP 67 mm Hg), heart rate 142 beats/minute, and CVP 8 mm Hg while receiving a norepinephrine (10 mcg/minute) infusion after intravenous fluid resuscitation. Norepinephrine has now been weaned off while maintaining a MAP of 67 mm Hg. Ceftriaxone 1 g intravenously every 24 hours and levofloxacin 750 mg intravenously every 24 hours have been initiated for community-acquired pneumonia. Which is the best therapeutic plan for the patient's ARDS?
   A. Continue fluid resuscitation to maintain a CVP of 10–14 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; prone positioning; and sedative administration to target deep sedation and cisatracurium infusion.
   B. Begin diuresis to target a CVP less than 4 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; supine positioning; and sedative administration to target deep sedation and cisatracurium infusion.
   C. Begin diuresis to target a CVP less than 4 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; supine positioning; and sedative administration to target deep sedation.
   D. Discontinue fluid resuscitation and begin diuresis to target a CVP less than 4 mm Hg while maintaining a MAP greater than 65 mm Hg; low tidal volume strategy of 4–8 mL/kg of ideal body weight; prone positioning; and sedative administration to target deep sedation and cisatracurium infusion.

Patient Cases *(continued)*

2. A 70-year-old woman (height 63 inches, weight 65 kg) is transferred to your ICU from an outside hospital after outside hospital admission for hypoxic respiratory failure. She had been treated for ARDS at the outside hospital for 3 days before her family requested hospital transfer. On admission, the patient is receiving MV with the following settings: SIMV mode, tidal volume 600 mL (12 mL/kg), respiratory rate 12 breaths/minute, PS 10 cm H_2O, and PEEP 10 cm H_2O. Which is the best therapy for her ARDS?
   - A. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O; supine positioning.
   - B. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O; prone positioning; cisatracurium administration.
   - C. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O; supine positioning; cisatracurium administration.
   - D. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O; prone positioning.

3. A 63-year-old woman (height 165 cm; total body weight 64 kg) with a medical history of insulin-dependent diabetes and chronic kidney disease was admitted to the general ward 2 days ago for acute COVID-19 pneumonia requiring oxygen therapy via nasal cannula. She was started on dexamethasone 6 mg oral daily. Today, she transferred to the intensive care unit following endotracheal intubation because of worsening oxygenation and meeting severe ARDS criteria. Lung-protective MV is initiated at tidal volume 340 mL, respiratory rate 22 breaths/minute, PEEP 12 cm H_2O, and F_{IO_2} 100%. Her arterial blood gas values are as follows: pH 7.28, Pa_{CO_2} 46 mm Hg, Pa_{O_2} 60 mm Hg, and HCO_3 24 mEq/L with Sa_{O_2} of 92%. Which is most appropriate therapeutic plan regarding her corticosteroids?
   - A. Discontinue dexamethasone 6 mg oral daily.
   - B. Change dexamethasone 6 mg oral daily to methylprednisolone 40 mg intravenous four times daily.
   - C. Change dexamethasone 6 mg oral daily to dexamethasone 6 mg intravenous daily.
   - D. Change dexamethasone 6 mg oral daily to dexamethasone 20 mg intravenous daily.

4. K.J. is a 56-year-old man (height 72 inches; total body weight 120 kg) admitted to the ICU for septic shock requiring vasoactive support and ARDS pneumonia. Lung-protective MV is initiated as follows: tidal volume 600 mL, respiratory rate 24 breaths/minute, PEEP 14 cm H_2O, and F_{IO_2} 100% with plateau pressure of 24 mm Hg. His arterial blood gas values are pH 7.28, Pa_{CO_2} 46 mm Hg, Pa_{O_2} 62 mm Hg, and HCO_3 24 mEq/L. Which of the following treatment strategies may be most appropriate at this time to improve oxygenation?
   - A. Inhaled nitric oxide.
   - B. ECMO.
   - C. Inhaled epoprostenol.
   - D. Cistracurium.

5. D.J. is a 49-year-old man with septic shock requiring vasoactive support and ARDS with MV at the following settings: tidal volume 400 mL, respiratory rate 26 breaths/minute, PEEP 20 cm H_2O, and F_{IO_2} 100%, resulting in a plateau pressure of 40 mm Hg. The patient's arterial blood gas values after mechanical ventilation initiation are as follows: pH 7.45, Pa_{CO_2} 34 mm Hg, Pa_{O_2} 110 mm Hg, and HCO_3 24 mmol/L with Sa_{O_2} 88%. Which of the following strategies is most appropriate at this time?
   - A. Cisatracurium, furosemide, and prone positioning.
   - B. Cistatracurium, furosemide, and ECMO.
   - C. Prone positioning, dexamethasone, and cisatracurium.
   - D. Prone positioning, dexamethasone, and ECMO.

II. INTUBATION

A. Endotracheal Intubation
   1. Provides access for suctioning of tracheobronchial secretions, maintains a patent airway, and allows administration of medications
   2. Indications include airway protection, facilitation of ventilation and oxygenation, assurance of airway patency, and induction of anesthesia for surgery.
   3. Orotracheal intubation is preferred for elective and emergency cases.
   4. Nasotracheal intubation is beneficial for patients undergoing maxillofacial surgery or dental procedures and for patients with limited mouth opening. This route may be associated with increased risk of bleeding and sinusitis. As a result, it should be avoided in patients with severe nasal or midface trauma.
   5. Complications include insertion trauma, gastric aspiration, hypoxemia, laryngospasm, esophageal intubation, right main bronchus intubation, cardiac arrhythmias, and hemodynamic impairment.

B. Rapid Sequence Intubation (RSI)
   1. Rapid and sequential administration of a rapid-acting induction agent and a NMBA to facilitate intubation and decrease the risk of aspiration
   2. Series of seven distinct steps: preparation, preoxygenation, pretreatment or more contemporarily preintubation optimization, induction either prior or with paralysis, protection and positioning, placement of the tube in the trachea, and management after intubation

C. Clinical Practice Guideline on Rapid Sequence Intubation
   1. These recently published guidelines were developed to provide evidence-based recommendations on pharmacologic and nonpharmacologic topics related to RSI (Critical Care Medicine 2023;51:1411-30).
   2. Overall, 10 clinically relevant guideline statements involving specific aspects of RSI were finalized; however, a summary of medication-related aspects of RSI are summarized below (Table 6).

Table 6. Clinical Practice Guideline Rapid Sequence Intubation Medication-Related Recommendations

RSI Step	Summary	GRADE Recommendation
Pretreatment	Not reported	Not reported
Induction	Suggest sedative-hypnotic induction agent when neuromuscular blocking agent will be used	Best practice statement (level of evidence not graded)
	No difference suggested between etomidate and other induction agents regarding outcomes (survival, hypotension risk, or need for vasoactive support)	Conditional (moderate level of evidence)
	Suggest against the use of corticosteroids following etomidate administration	Conditional (low level of evidence)
Paralysis	Recommend administering neuromuscular blocking agent following induction	Strong (low level of evidence)
	Suggest administering either rocuronium or succinylcholine (if no contraindications)	Conditional (low level of evidence)

RSI = rapid sequence intubation.

D. Pretreatment or Preintubation Optimization

1. Occurs before an induction agent or NMBA is administered
2. Pretreatment attenuates the sympathetic and parasympathetic responses (catecholamine release, hypertension, tachycardia, potentially increased ICP in patients with impaired cerebral autoregulation) to laryngoscopy. However, because of low quality of evidence and lack of demonstration of benefit to the patient, this step is more commonly omitted.
3. Fentanyl or lidocaine can be used as a pretreatment medication (Table 7).
4. Atropine and defasciculating doses of nondepolarizing NMBAs are not recommended for routine use in RSI for adult patients.
5. More contemporarily, this step may be called "preintubation optimization," which involves stabilization of hemodynamic parameters and creation of mitigation strategies for other possible complications (*Am J Health Syst Pharm*. 2023;80(4):182-195).

Table 7. Pretreatment Agents

Agent	Dose	Onset	Duration	Advantages	Disadvantages
Fentanyl	IV: 1–3 mcg/kg	< 30 s	0.5–1 hr	• Blunts hypertensive response from intubation • Recommended over other opioids because of its rapid onset and short duration of action	• Chest wall rigidity (doses > 100 mcg/kg) • Hypotension, bradycardia, and respiratory depression
Agent	**Dose**	**Onset**	**Duration**	**Advantages**	**Disadvantages**
Lidocaine	IV: 1.5 mg/kg	45–90 s	10–20 min	• May prevent increase in ICP through blunting of cough reflex • May reduce bronchospasm in patients with reactive airway disease	• Contraindicated in patients with an amide anesthetic allergy, bradycardia, or severe heart block

ICP = intracranial pressure; IV = intravenous(ly).

E. Induction Agents

1. Given as rapid intravenous push immediately before the paralyzing agent to help achieve optimal conditions for intubation
2. Agents should provide rapid loss of consciousness, analgesia, amnesia, and stable hemodynamics.
3. Agents used for induction during RSI include barbiturates, benzodiazepines (midazolam), etomidate, ketamine, and propofol (Table 8).
4. Barbiturates
    a. Thiopental is no longer available in the United States.
    b. Methohexital is rarely used because of its adverse effect profile, including respiratory depression, hypotension, and histamine release.
5. Etomidate
    a. A nonbarbiturate, imidazole derivative with a rapid onset of action and a very short elimination half-life
    b. Enhances the effects of γ-aminobutyric acid, thereby blocking neuroexcitation and inducing unconsciousness (does not provide analgesia)
    c. Transiently inhibits the conversion of cholesterol to cortisol by inhibiting 11ß-hydroxylase, leading to transient adrenal suppression

i. No convincing or consistent evidence suggests that etomidate is associated with an increased risk of death (Intensive Care Med 2011;37:901-10; Chest 2015;147:335-46).

ii. Large randomized, prospective, adequately powered studies are needed to clarify the clinical significance of etomidate's effects in patients at risk of adrenal insufficiency.

Table 8. Induction Agents

Agent	Dose	Onset	Duration	Advantages	Disadvantages
Etomidate	IV: 0.2–0.6 mg/kg	10–20 s	4–10 min	• Minimal cardiovascular effects • Decreased ICP with minimal effects on cerebral perfusion	• Myoclonic jerks • Transient decrease in cortisol production
Ketamine	IV: 1–2 mg/kg IM: 4–10 mg/kg	IV: 10–15 s IM: 3–4 min	IV: 5–15 min IM: 12–25 min	• Catecholamine reuptake inhibition (transient increase in blood pressure and heart rate) • Respiration and airway reflexes maintained • Does not increase ICP • Relieves bronchospasm • Has both amnestic and analgesic effects	• Negative inotropic/chronotropic effects (in catecholamine-depleted patients) • Emergence delirium, nightmares, and hallucinations (premedication with a benzodiazepine does not reduce the incidence)
Midazolam	IV or IM: 0.2–0.3 mg/kg	60–90 s	1–4 hr	• Recommended over other benzodiazepines because of its relatively faster onset of action	• Compared with other induction agents, slower onset and longer duration • Dose-dependent respiratory depression and hypotension
Propofol	IV: 1.5–2.5 mg/kg	15–45 s	3–10 min	• Decreases ICP; however, may also decrease CPP • Mild bronchodilating effects • Drug of choice in pregnancy	• Hypotension and bradycardia • Negative inotropic effects

CPP = cerebral perfusion pressure; IM = intramuscular(ly).

F. NMBAs
1. Block impulse transmission at the neuromuscular junction, resulting in skeletal muscle paralysis
2. Used immediately after induction to help achieve optimal conditions for intubation
3. Have no sedative, analgesic, or amnestic properties
4. Problematic in patients with a difficult or failed airway
5. Depolarizing NMBAs (Table 9)
   a. Succinylcholine: Noncompetitively binds to acetylcholine receptors, leading to sustained depolarization of the neuromuscular junction and prevention of muscle contraction
   b. Preferred agent for RSI
6. Nondepolarizing NMBAs (Table 9)
   a. Rocuronium and vecuronium: Competitive antagonists of acetylcholine at the neuromuscular junction, leading to the prevention of muscle contraction
   b. Intermediate-acting nondepolarizing agents are alternatives when succinylcholine is contraindicated.
   c. Usually have a slower onset of action and longer duration of action

7. Reversal of nondepolarizing NMBAs with a failed airway
   a. An acetylcholinesterase inhibitor (neostigmine or pyridostigmine) in combination with an anticholinergic (atropine or glycopyrrolate)
   b. Sugammadex binds the aminosteroid class of nondepolarizing NMBAs (vecuronium and rocuronium).

Table 9. Common Neuromuscular Blocking Agents

Agent	Dose	Onset	Duration	Cautions
Succinylcholine	IV: 1–2 mg/kg IM: 3–4 mg/kg (max 150 mg)	IV: 1 min IM: 2–3 min	IV: 3–5 min IM: 10–30 min	• Prolonged effects in pseudocholinesterase deficiency • Hyperkalemia or patients at risk of hyperkalemia (prolonged immobilization, crush injuries, myopathies, burns, muscular dystrophy, stroke, and spinal cord injuries) • Malignant hyperthermia • Bradycardia/hypotension with repeated doses • Mild increase in ICP
Rocuronium	IV: 0.6–1.2 mg/kg	1–2 min	30–60 min	• Moderate increase in duration with liver dysfunction, minimal increase in duration with renal dysfunction
Vecuronium	IV: 0.08–0.1 mg/kg	2–3 min	20–60 min	• Prolonged duration in renal and liver dysfunction

G. Management After Intubation
   1. Provide continued sedation/analgesia as needed if an intermediate-acting NMBA was used and assists in adequate oxygenation and ventilation
   2. Minimize long-term use of analgesics and sedatives
   3. Maintain head-of-bed elevation at 30–45 degrees
   4. Mouth and eye care
   5. Bowel regimen
   6. Stress ulcer and deep vein thrombosis prophylaxis

Patient Cases

6. A 55-year-old man (weight 75 kg) is admitted to the burn ICU after a 65% total body surface area burn to the abdomen, back, and lower extremities from a house fire. He is unconscious and unable to protect his airway. His medical history is significant for hypertension and hyperlipidemia. He is currently receiving high-dose norepinephrine and vasopressin to maintain a MAP of 65 mm Hg. His current laboratory test results show the following: sodium (Na) 130 mEq/L, potassium (K) 5.9 mEq/L, chloride (Cl) 122 mEq/L, carbon dioxide (CO_2) 15 mg/dL, blood urea nitrogen (BUN) 10 mg/dL, and serum creatinine (SCr) 1.3 mg/dL. Which group of medications would be most appropriate for RSI?
   - E. Fentanyl, propofol, rocuronium.
   - F. Fentanyl, ketamine, succinylcholine.
   - G. Fentanyl, etomidate, rocuronium.
   - H. Fentanyl, propofol, succinylcholine.

7. A 39-year-old homeless man (weight 70 kg) was admitted to the neurosciences ICU with a traumatic head injury after falling off a 3-ft ladder while intoxicated. Imaging reveals a subdural hematoma. The team decides to intubate this patient. His current laboratory values are as follows: Na 133 mEq/L, K 4.5 mEq/L, Cl 97 mEq/L, CO_2 28 mg/dL, BUN 13 mg/dL, SCr 0.7 mg/dL, and glucose 140 mg/dL. Which induction medication would be most appropriate to use for RSI?
   - I. Propofol 90 mg intravenous push.
   - J. Ketamine 100 mg intravenous push.
   - K. Midazolam 15 mg intravenous push.
   - L. Etomidate 150 mg intravenous push.

III. MECHANICAL VENTILATION

A. Critical to Understanding How MV Works: A fundamental knowledge of acid-base disorders and normal respiratory physiology

B. Two Essential Categories of Respiratory Failure: Hypercapnic and hypoxemic. Derangements in Pa_{O_2} or Pa_{CO_2} will help determine the cause of respiratory failure. (Table 10 provides the context for normal oxygenation and ventilation values.)

C. Modes
   1. Assist control (AC) ventilation
      a. Volume control (VC)
         i. The patient receives a predetermined respiratory rate and tidal volume, with additional patient-initiated breaths provided at the preset tidal volume. Patient-initiated respiration generates a negative pressure within the ventilator circuit, which is sensed by the ventilator, and a full tidal volume breath is provided.
         ii. Potential for ventilator dyssynchrony, “double-stacking,” and respiratory alkalosis
         iii. Mode used in the ARDSNet trial of tidal volume strategy to limit spontaneous tidal volumes (N Engl J Med 2000;342:1301-8)
      b. Pressure control
         i. The patient will receive a breath at a fixed rate until a predetermined peak pressure limit is reached. The tidal volume is variable and limited by the peak pressure limit.
         ii. Not ideal for patients with low minute ventilation and may lead to hypoventilation and further hypoxia

2. Synchronized intermittent mandatory ventilation (SIMV): Patients will receive a predetermined respiratory rate and tidal volume plus additional spontaneous, self-generated breaths at whatever tidal volume they can generate. Not ideal for the treatment of ARDS, given patients' ability to exceed the present tidal volume for spontaneous breaths in excess of 6 mL/kg
3. PS ventilation
    a. Usually used as a weaning mode of MV from a more intensive mode of MV (i.e., AC ventilation)
    b. The patient initiates each breath with assistance from the ventilator in the form of a preset pressure value. The ventilator is set to provide a correct amount of pressure to assist with each inspiratory effort. The tidal volume and respiratory rate depend on the patient.

D. Ventilator Variables (*Pharmacotherapy. 2007;27:250-266*)
1. F_{IO_2}
    a. Amount of oxygen that is delivered with each breath, from 21% to 100% at sea level
    b. F_{IO_2} is generally tapered to provide the minimal oxygenation needed to meet patient needs. Concerns for oxygen toxicity with high F_{IO_2} requirements over prolonged period
2. Tidal volume
    a. Volume of air inspired in a breath (delivered by MV or spontaneously)
    b. Set according to oxygenation and ventilation requirements. Patients with ARDS are treated with a low tidal volume strategy.
3. Respiratory rate
    a. Set to provide a minimal number of breaths from the ventilator at the set tidal volume
    b. Titrated by minute ventilation, Pa_{CO_2}, and pH. Minute ventilation (liters per minute) = tidal volume (liters) × respiratory rate (breaths/minute).
4. Flow rate
    a. Velocity of air delivered
    b. Velocity is greatest initially upon inspiration and decelerates toward the end of the inspiratory effort.
5. PEEP
    a. Positive pressure in the alveoli during expiration
    b. Pressure at the end of expiration promotes alveoli recruitment while minimizing the risk of collapse in ARDS.
    c. Titrated with F_{IO_2} to provide the minimum necessary support to meet the patient's oxygenation requirements

Table 10. Normal Respiratory Physiology Values

Value	Normal Range
Tidal volume (mL/kg)	5–10
Respiratory rate (breaths/min)	12–20
Minute ventilation (L/min)	5–10
Pa_{CO_2} (mm Hg)	35–45
Pa_{O_2} (mm Hg)	80–100
Sa_{O_2} (%)	95–100

Patient Case

8. A 74-year-old woman (height 63 inches, weight 65 kg) is transferred to your ICU from an outside hospital after admission for hypoxic respiratory failure. She had been treated at the outside hospital for ARDS for 3 days before her son requested transfer. When the patient arrives in your ICU, she is receiving MV with the following settings: SIMV mode, tidal volume 600 mL (12 mL/kg), respiratory rate 12 breaths/minute, PS 10 cm H_2O, and PEEP 10 cm H_2O. Which is the best ventilator plan for treating her ARDS?

   M. AC/VC mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O.
   N. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O.
   O. PS mode, PS 10 cm H_2O, PEEP 5 cm H_2O.
   P. SIMV mode, tidal volume 300 mL (6 mL/kg), respiratory rate 10 breaths/minute, PS 10 cm H_2O, PEEP 5 cm H_2O.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**

The patient has early severe ARDS (for less than 48 hours and Pa_{O_2}/F_{IO_2} less than 150 mm Hg) and hemodynamic stability (post-resuscitation MAP greater than 65 mm Hg). According to the findings of an ARDSNet-sponsored multicenter trial, he would qualify for conservative fluid management (CVP less than 4 mm Hg). In addition, vasopressors should be discontinued and diuresis initiated to achieve a target CVP less than 4 mm Hg (Answer A is incorrect). Given the timing and the severity of the patient's ARDS, he should be placed in the prone position (Answers B and C are incorrect). In addition, this patient would qualify for a cisatracurium infusion. Given the timing and severity of his ARDS, he qualifies to receive a lung-protective ventilation strategy (tidal volume 4–6 mL/kg of ideal body weight) and diuresis to a CVP less than 4 mm Hg (hemodynamically stable if weaned off vasopressors) while placed in the prone position and administered a cisatracurium infusion (Answer D is correct).

2. **Answer: A**

The patient presents to your ICU after 3 days of care. Therefore, she does not currently meet the criteria for being administered cisatracurium or placed in the prone position (Answers B–D are incorrect). Currently, the applicable therapy to apply is a lung-protective ventilation strategy (tidal volume 4–6 mL/kg of ideal body weight) (Answer A is correct).

3. **Answer: C**

The patient was appropriately started on corticosteroids for COVID-19 pneumonia during the same hospital admission prior to developing ARDS and subsequently transferred to the ICU. Dexamethasone was associated with favorable results among COVID-19 hospitalized patient requiring oxygen support (both noninvasive and invasive mechanical ventilation) as well as critically ill patients with moderate to severe ARDS; therefore, continuing dexamethasone is appropriate (Answer A is incorrect). Methylprednisolone has not been associated with favorable clinical outcomes among COVID-19 or moderate to severe ARDS patients (Answer B is incorrect). Although the DEXA-ARDS trial found improved clinical outcomes associated with the dexamethasone 20 mg daily (followed by 10 mg daily) regimen in ARDS patients, it is important to recognize this patient population did not consist of COVID-19. Furthermore, a meta-analysis evaluating various corticosteroid regimens failed to find any benefit of higher dexamethasone dosing strategies (i.e., 20 mg daily) compared with lower doses (6 mg daily) (Answer C is correct; Answer D is incorrect).

4. **Answer: B**

Although selective pulmonary vasodilating agents may modestly improve oxygenation parameters at best, they have not shown to improve clinical outcomes. Their role in therapy is uncertain, but it may be mostly considered salvage therapy after failing more proven strategies (Answers A and C are incorrect). The role of neuromuscular blocking agents in ARDS remain controversial. However, the ROSE clinical trial failed to corroborate any improved clinical outcomes previously demonstrated (ACURASYS trial). Cisatracurium may not be appropriate at this time since plateau pressures remain acceptable despite using high PEEP (Answer D is incorrect). ECMO use in ARDS also remains controversial. However, severe ARDS may be a compelling reason to initiate ECMO compared with alternative supportive therapies (Answer B is correct).

5. **Answer: C**

ECMO may not be the most appropriate strategy at this time considering the patient has moderate to severe ARDS with corresponding Pa_{O_2} of 110 mm Hg on lung protective mechanical ventilation alone (Answers B and D are incorrect). Furosemide may not be the most appropriate strategy because the patient is currently requiring vasoactive support (Answers A and B and incorrect). Cisatracurium may be indicated for this patient considering the plateau pressure is elevated as well as prone positioning to help improve oxygenation with suboptimal parameters on mechanical ventilation along; furthermore, corticosteroids may also be indicated given ARDS severity and timing (Answer C is correct).

6. **Answer: C**

Propofol, ketamine, and etomidate can all be used for induction. Propofol may worsen hypotension; therefore, because this patient is already receiving vasoactive medications to maintain his blood pressure, propofol would not be ideal (Answer A is incorrect). Succinylcholine causes the up-regulation of acetylcholine receptors, predisposing the muscle fibers to release excess potassium because they are depolarized, which leads to significant dysrhythmias or cardiac arrest (Answers B and D are incorrect). Appropriate induction and neuromuscular blockade in this patient would be to administer etomidate (indicated for hemodynamically unstable patients), fentanyl (providing adequate analgesia), and rocuronium (does not increase serum potassium) (Answer C is correct).

7. **Answer: B**

Although propofol may promptly lower ICP, it can also induce hypotension and thus decrease cerebral perfusion pressure (Answer A is incorrect). Midazolam could be used as an induction agent; however, it is not the best agent for RSI because of its delayed onset of action (Answer C is incorrect). Etomidate may be considered in the setting of increased ICP; however, the dose in this case is too high (Answer D is incorrect). Ketamine not only decreases ICP but also prevents fluctuations in ICP (Answer B is correct).

8. **Answer: A**

After recognizing that the patient has ARDS, a lung-protective ventilation strategy should be implemented (tidal volume 4–6 mL/kg). Choosing a PS or SIMV mode would allow the patient to initiate spontaneous breaths in excess of the goal tidal volume (Answers B–D are incorrect). In the ARDSNet study of tidal volume strategy, the AC mode was most commonly used to promote the application of low tidal volumes (Answer A is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: B**

According to the Berlin ARDS definition, the category of acute lung injury was removed in favor of categorizing the severity of ARDS ($Pa{O_2}/F{IO_2}$ less than 200 mm Hg) (Answer A is incorrect). Because of the relative difference in mortality rates, mild and moderate ARDS cases are less likely to benefit from therapeutic interventions, given the number needed to treat to show an effective intervention (Answers C and D are incorrect). In the trials evaluating prone positioning and cisatracurium, patients with severe ARDS were the most likely to benefit. Although the criteria used for severe ARDS in these studies differed from those used in the Berlin definition (both studies were initiated before publication of the Berlin ARDS definition), a post hoc analysis shows a survival benefit in favor of the group with the highest mortality rate (Answer B is correct).

2. **Answer: C**

The Belin definition defines ARDS severity with $Pa{O_2}/F{IO_2}$ as one element of criteria. Comprehension of subpopulations of ARDS is essential to apply published clinical data among various therapies. Although not universally defined, the most commonly reported inclusion criteria among landmark ARDS clinical trials (ROSE, ACURASYS, DEXA-ARDS, etc.) was moderate to severe ARDS criteria defined as $Pa{O_2}/F{IO_2}$ less than 150 mm Hg (Answer C is correct; Answers A and B are incorrect). Also, these trials did not define a lower limit of ARDS severity (e.g., 50–150 mm Hg) as inclusion criteria (Answer D is incorrect).

3. **Answer: B**

The landmark ARDSNet trial evaluating lung protective mechanical ventilation strategies defined low tidal volumes ranging from 4 to 8 mL/kg using predicted body weight (also known as ideal body weight (Answer B is correct). Total body weight may overestimate ventilation requirements in adult patients with obesity because lung volume is unrelated to increasing total body weight (i.e., lung size remains relatively constant irrespective of adult body mass) (Answers A, C, and D are incorrect).

4. **Answer: B**

This patient has both ARDS and septic shock. In addition, he has likely had ARDS for less than 48 hours; therefore, the time to initiation of several treatments is essential. The patient is actively in shock (as evidenced by his blood pressure), thus making a fluid-conservative strategy (CVP less than 4 mm Hg) impossible (Answer C is incorrect). Because the time to presentation is less than 48 hours and the patient has severe ARDS, he meets the criteria for cisatracurium administration and prone positioning, and a treatment plan should include these two therapies (Answers A and D are incorrect). A therapy plan should include shock resuscitation (fluid-liberal strategy, CVP 10–14 mm Hg), lung-protective ventilation (tidal volume 4–8 mL/kg of ideal body weight), prone positioning, and cisatracurium administration (Answer B is correct).

5. **Answer: D**

The FACTT Lite approach attempts to simplify fluid management for implementation among ARDS patients in clinical practice. The parameters used to determine clinical course of action (remove fluid with diuretic administration, administer fluid boluses, or monitor without administration of either therapy) include MAP, urine output, and CVP (pulmonary arterial occlusion pressure may be optional based on institutional practices for invasive monitoring). Administering fluids in this patient may not be the most appropriate approach because MAP, CVP, and urine output do not suggest hypovolemia (Answer C is incorrect). Although continuous infusion furosemide may be an option within this published protocol, it is important to note that both the suggested rate of infusion and the time to re-evaluate are inconsistent with the FACTT Lite protocol. Re-evaluation should be relatively short irrespective of the clinical decision-making (i.e., 1 or 4 hours) (Answer B is incorrect). It is important to emphasize that the conservative management approaches defined in this protocol require the patient achieve a MAP of 60 mm Hg without any vasoactive support for at least 12 hours. The short time period since vasopressor support cessation may be too aggressive to administer without demonstrating clinical stable hemodynamic pressures (Answer A is incorrect). The most appropriate approach would be monitoring until adequate MAP has been achieved without vasoactive support for at least 12 hours (Answer D is correct).

6. **Answer: A**

The DEXA-ARDS clinical trial has been the only contemporary trial evaluating corticosteroids (dexamethasone) among ARDS patients already receiving lung-protective mechanical ventilation strategies (Answer A is correct). Despite the numerous ARDS trials evaluating methylprednisolone, none have concurrently evaluated with lung-protective strategies among all study patients (Answer C is incorrect). Despite the optimal timing of corticosteroid use in ARDS remains controversial, dexamethasone was started "early" after ARDS onset in the DEXA-ARDS trial (Answer B is incorrect). The LaSRS clinical trial found increased risk of death in the steroid group compared with controls among patients enrolled greater than 14 days after ARDS onset. Unfortunately, this unadjusted subgroup analysis may have biased these findings. Subsequent re-evaluation of these results found no differences in mortality among in this subgroup. Furthermore, "late" (greater than 5–7 days) corticosteroid use in ARDS has not consistently demonstrated worse outcomes (Answer D is incorrect).

7. **Answer: D**

Neuromuscular blocking agents should always be administered after induction agents (Answers A, B, and C are incorrect). In addition, atropine is not routinely recommended (Answer C is incorrect) for RSI in adult patients. Atropine should be kept nearby for patients who are at an increased risk of bradycardia during RSI (use of β-blockers, calcium channel blockers, digoxin, or amiodarone). Induction agents (and pretreatment medications) should be administered before NMBAs (Answer D is correct).

8. **Answer: B**

The patient has moderate to severe ARDS. The initial MV strategy is using low tidal volumes (Answers A and C are incorrect). Considering the patient is hemodynamically stable without requiring vasoactive support, conservative fluid management approaches are warranted (Answer B is correct). Hemodynamically unstable patients may be candidates for liberal fluid management strategies (Answer D is incorrect).

Pulmonary Disorders II

Zachary R. Smith, Pharm.D., FCCP, FCCM, BCPS, BCCCP

Henry Ford Hospital
Detroit, Michigan

PULMONARY DISORDERS II

ZACHARY R. SMITH, PHARM.D., FCCP, FCCM, BCPS, BCCCP

HENRY FORD HOSPITAL
DETROIT, MICHIGAN

Learning Objectives

1. Design a treatment plan for a cystic fibrosis (CF) exacerbation.
2. Develop a pharmacotherapy plan for pulmonary artery hypertension using a risk assessment–based strategy.
3. Describe classifications and risk factors for increased severity of asthma exacerbation and treatment plans for patients with acute respiratory failure caused by asthma exacerbation.
4. Recognize evidence-based treatment options for acute exacerbations of chronic obstructive pulmonary disease (COPD).

Abbreviations in This Chapter

ABG	Arterial blood gas
AC/VC	Assist control/volume control
BNP	B-type natriuretic peptide
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CTEPH	Chronic thromboembolic pulmonary hypertension
CVP	Central venous pressure
ECOPD	Exacerbation of chronic obstructive pulmonary disease
ED	Emergency department
ET	Endothelin
ERA	Endothelin receptor antagonist
FEV_1	Forced expiratory volume in the first second of expiration
Fio_2	Fraction of inspired oxygen
ICU	Intensive care unit
MDI	Metered dose inhaler
mPAP	Mean pulmonary artery pressure
MV	Mechanical ventilation
Paco_2	Partial pressure of carbon dioxide
Pao_2	Partial pressure of oxygen
PAH	Pulmonary artery hypertension
PCWP	Pulmonary capillary wedge pressure
PDE5i	Phosphodiesterase type 5 inhibitor
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RV	Right ventricular
SABA	Short-acting β-agonist
Sao_2	Oxygen saturation
Spo_2	Functional oxygen saturation
6MWD	6-minute walk distance

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. A 21-year-old woman (height 62 inches, weight 50 kg) with a medical history significant for cystic fibrosis (CF) is admitted to the intensive care unit (ICU) with acute respiratory failure requiring mechanical ventilation (MV). After intubation, her arterial blood gas (ABG) results are as follows: pH 7.27, Paco_2 45 mm Hg, bicarbonate 22 mEq/L, Pao_2 55 mm Hg, and oxygen saturation (Sao_2) 88%. Her ventilator settings are as follows: assist control/volume control (AC/VC) mode, tidal volume 300 mL (6 mL/kg), respiratory rate 20 breaths/minute, fraction of inspired oxygen 60%, pressure support 5 cm H_2O, and positive end-expiratory pressure (PEEP) 5 cm H_2O. Her blood pressure is 110/70 mm Hg and heart rate is 95 beats/minute. Which is the best holistic therapy plan?
   A. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 150 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a central venous pressure (CVP) goal of 10–14 mm Hg; dornase alfa and hypertonic saline 7% nebulization.
   B. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 500 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a CVP goal of 10–14 mm Hg; dornase alfa and hypertonic saline 7% nebulization.
   C. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 150 mg intravenously every 8 hours; intravenous fluid resuscitation to maintain a CVP goal of 10–14 mm Hg.
   D. Initiate cefepime 2 g intravenously every 8 hours and tobramycin 500 mg intravenously every 24 hours; diuresis to maintain a CVP goal of less than 4 mm Hg while mean arterial pressure is greater than 65 mm Hg; dornase alfa and hypertonic saline 7% nebulization.

2. Which adjunctive measure for a CF exacerbation has the highest quality of evidence for improving patient outcomes?
   - A. Normal saline (0.9%) nebulization.
   - B. Corticosteroid administration.
   - C. Concurrent administration of intravenous and inhaled antibiotics.
   - D. Aggressive chest physical therapy.

3. A 55-year-old woman with pulmonary artery hypertension (PAH) is admitted to the ICU for severe respiratory failure. She reports increased work of breathing for the past 5 days and full adherence to her PAH medication regimen, which includes macitentan 10 mg daily and sildenafil 40 mg three times daily. Her current vital signs are as follows: blood pressure 76/60 mm Hg, heart rate 140 beats/minute, respiratory rate 30 breaths/minute, and 85% Sao_2 on 6 L of nasal cannula. Right heart catheterization reveals the following: mean pulmonary artery pressure (mPAP) 50 mm Hg, right atrial pressure 25 mm Hg, cardiac index 1.9 L/minute/m^2, and pulmonary capillary wedge pressure (PCWP) 16 mm Hg. A transthoracic echocardiogram reveals an ejection fraction of 60% with severe right ventricular (RV) dilatation. Which regimen would be most appropriate for this patient?
   - A. Dopamine infusion.
   - B. Epoprostenol infusion.
   - C. Phenylephrine infusion.
   - D. Furosemide intravenous push.

4. Which best describes one of the primary treatment goals for the management of PAH?
   - A. Achieve and maintain WHO functional class (FC) III or IV.
   - B. Preserve 6-minute walk distance (6MWD) to greater than 300 m.
   - C. Preserve RV size and function (right atrial pressure less than 8 mm Hg).
   - D. Normalize B-type natriuretic peptide (BNP) (less than 200 ng/L).

5. A 42-year-old man presents to the emergency department (ED) with anxiety and shortness of breath. Auscultation reveals audible wheezing. He has difficulty speaking in full sentences. He has used his albuterol metered dose inhaler (MDI) at home for the past several hours without symptom resolution. His forced expiratory volume in the first second of expiration (FEV_1) is 35% of predicted. Which best classifies this patient's asthma exacerbation?
   - A. Mild.
   - B. Moderate.
   - C. Severe.
   - D. Life threatening.

6. A 55-year-old man presents to the ED with a 2-week history of progressive shortness of breath, wheezing, and dyspnea at rest. He is confused and speaking in short phrases but can indicate that his inhaled bronchodilator has failed to improve his symptoms for the past 2 days. He is afebrile with heart rate 116 beats/minute, respiratory rate 32 breaths/minute, and Sao_2 86% on room air. He is placed on supplemental oxygen and administered albuterol nebulization and methylprednisolone 125 mg intravenously × 1. One hour later, his oxygenation has not improved. Which adjunctive therapy would be best to add to his current regimen?
   - A. Antimicrobial agents directed at community-acquired pathogens.
   - B. Magnesium sulfate 2 g intravenously over 20 minutes.
   - C. Theophylline 4.6 mg/kg intravenous loading dose; then obtain serum concentration in 30 minutes to guide further dosing.
   - D. Acetylcysteine 20% 3 mL, nebulized every 6 hours.

7. A 66-year-old man presents to the ICU with acute respiratory failure from a chronic obstructive pulmonary disease exacerbation (ECOPD). He has had no exacerbations in the past 2 years. His home medications include albuterol hydrofluoroalkane 2 puffs four times daily as needed and tiotropium 1 puff once daily. The patient denies any recent sick contacts or changes in sputum production. He has no known drug allergies. He is placed on 3 L of nasal cannula (Sao_2 97%) and inhaled albuterol and ipratropium by nebulization. Which other therapy would be most appropriate for this patient?

   A. Azithromycin 500 mg intravenously daily.
   B. Prednisone 40 mg orally daily.
   C. Levofloxacin 500 mg orally daily.
   D. Methylprednisolone 125 mg intravenously every 6 hours.

8. A 65-year-old Black man (height 177.8 cm, weight 90 kg, SCr 1.5 mg/dL) presents with a medical history of end-stage renal disease on dialysis, COPD, hypertension, and hyperlipidemia. He is admitted from home to the ICU with respiratory failure. His symptoms before admission included shortness of breath, cough, increased sputum production, purulence, and fever. His respiratory viral panel is positive for rhinovirus. His Sao_2 is 85% on room air; he is placed on high-flow nasal cannula (HFNC) 40 L/minute, fraction of inspired oxygen (Fio_2) 60%. The patient's work of breathing decreases, and after 15 minutes, his Sao_2 is 97%. He is continued on the same HFNC settings. He has been administered methylprednisolone 60 mg intravenously once and azithromycin 500 mg intravenously once. Which best depicts the current intervention for this patient that has demonstrated an increase in mortality?

   A. Corticosteroid dose higher than prednisone 40 mg oral equivalent.
   B. Titration of oxygen to peripheral Sao_2.
   C. Azithromycin dose greater than 250 mg.
   D. Maintaining Sao_2 greater than 92%.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1-4
    b. Task B: 2, 3
2. Domain 2: Therapeutics and Patient Management
    a. Task A: 1–3, 6, 8
    b. Task B: 1, 2, 12–14
    c. Task C: 1, 4
3. Domain 3: Professional Practice
    a. Task A: 1
    b. Task B: 1

I. CYSTIC FIBROSIS

A. Cystic Fibrosis (CF) – Chronic disease process that affects many organs, including the pancreas, liver, and intestine, but primarily the lung (Chest 2004;125:1-39)
  1. CF is a recessive disorder caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR controls the movement of chloride and bicarbonate across the cell membranes of many organs throughout the body (e.g., lungs, gastrointestinal tract, pancreas) (Chest 2018;154:383-93).
  2. Dysfunction of the CFTR within the airways also affects the ability of the airway membranes to absorb sodium and fluid through the epithelial sodium channel (ENaC), which creates a viscous mucus (Chest 2018;154:383-93). The pH of this mucus is more acidic, which impairs ciliary clearance and the function of phagocytic cells (Int J Mol Sci 2022;23:3513).
  3. Chronic therapy has been developed to target specific CFTR mutations, and such therapies may be seen in the ICU as home medications. Several of these agents have important drug-drug interactions as either substrates or inducers of CYP3A4 (Chest 2018;154:383-93).
  4. Social Determinants of Health in CF (Expert Rev Respir Med 2016;10:967-77)
    a. The term *socioeconomic status*, defined as access to education, material goods and services, social support, and position in society, contributes to differences in outcomes among patients with CF through varying exposure to allergens, quality of nutrition, chronic stress levels, and ability to self-manage disease, as well as access to medical care.
    b. Patients of a lower socioeconomic status have higher morbidity and mortality rates. Their disease progression related to lung function and nutrition are adversely affected as well.

B. Pulmonary Exacerbations of CF
  1. Definitions and significance
    a. There is no universally accepted definition for pulmonary exacerbations of CF (Respir Care 2020;65:233-51).
    b. Acute exacerbations include symptoms of increased cough, sputum production, shortness of breath, weight loss, and a decline in lung function.
    c. Pulmonary exacerbations of CF can have a significant impact on quality of life and disease progression. About 25% of patients with an exacerbation will not completely recover lung function at three months (Am J Respir Crit Care Med 2010;182:627-32).
  2. Common bacterial organisms (most common to least common)
    a. *Staphylococcus aureus* is the most common organism isolated from birth to teenage years.
    b. Methicillin resistant *Staphyloccocus aureus* (MRSA) becomes more common in the 11–30 years of age range.
    c. *Pseudomonas aeruginosa* has a prevalence rate of around 15% from birth to teenage years, but rapidly increases in prevalence after 17 years of age. Greater than 60% of adults with CF in the United States are infected with *P. aeruginosa*.
    d. *Haemophilus influenzae*
    e. *Stenotrophomonas maltophilia*
    f. *Achromobacter xylosoxidans*
    g. *Burkholderia cepacia complex*
    h. *Nontuberculous mycobacteria*
  3. Antibiotic therapy for pulmonary exacerbations of CF
    a. Antibiotic dosing is challenging because of the altered pharmacokinetics in patients with CF. Patients with CF can be distinguished by their large volume of distribution and augmented renal clearance.

b. Notably, most pulmonary exacerbations are not due to the acquisition of a new microorganism, and patients with CF commonly have routine cultures collected throughout their care. Using the patient's previous susceptibility pattern or restarting a previous successful antibiotic regimen is common practice.
   i. For patients with history of or suspected infection with *Pseudomonas aeruginosa*, initial treatment with two antipseudomonal agents is recommended, despite limited evidence that this practice improves outcomes (Am J Respir Crit Care Med 2009;180:802-8; Cochrane Database Syst Rev 2021;6:CD002007).
   ii. Two drugs from different classes are recommended rather than double β-lactams, with most data supporting a β-lactam in combination with an aminoglycoside, although toxicity risk and patient-specific factors should be taken into account.
   iii. Aggressive dosing of β-lactam antibiotics is recommended to optimize time above the minimum inhibitory concentration, primarily based on pharmacokinetic data. Current evidence is insufficient to recommend routine use of extended infusion or continuous infusion β-lactams for all patients with CF, but this practice should be considered on a case-by-case basis and is reasonable to utilize in critically ill patients with CF (Pharmacotherapy 2023;43:740-77; Respir Care 2009;54:522-37).
   iv. Extended-interval aminoglycoside dosing (e.g., once-daily dosing of tobramycin 10 mg/kg, targeting a peak concentration of 20–30 mg/L and a trough concentration of less than 1 mg/L) is as effective as conventional dosing, with possibly less nephrotoxicity (Lancet 2005;365:573-8; Cochrane Database Syst Rev 2017;3:CD002009).

c. Evidence is currently lacking for or against the simultaneous administration of inhaled and intravenous antibiotics for acute CF exacerbations (Table 1) (Am J Respir Crit Care Med 2009;180:802-8; Cochrane Database Syst Rev 2022;8:CD008319.

Table 1. Chronic Antimicrobial Therapy

Therapy	Clinical benefit(s)
Inhaled tobramycin[a]	• Improves lung function • Improves quality of life • Reduces exacerbations
Inhaled aztreonam[a]	• Improves lung function • Improves quality of life
Oral azithromycin[a]	• Improves lung function • Reduces exacerbations
Oral azithromycin[b]	• Reduces exacerbations

[a]Patients with history of *Pseudomonas aeruginosa*.

[b]Patients without history of *P. aeruginosa*.

Information from: Ann Am Thorac Soc 2014;11:1640-50

4. Duration of therapy
   a. A 10- to 14-day course of antibiotics is common practice, and durations are primarily driven by clinical response, either symptomatology or FEV_1 measurements.
   b. The Standardized Treatment of Pulmonary Exacerbation (STOP) trial reflected this precedent with a mean duration of intravenous antibiotics in adults of 16.2 days (J Cyst Fibros 2017;16:600-6).
   c. The STOP2 trial excluded ICU patients, but identified that for patients who improved within 7–10 days, 10 days of antibiotics was noninferior to 14 days. Patients without improvement should complete a 14-day course, but treating past 14 days was noninferior to a 21-day treatment course (Am J Respir Crit Care Med 2021;204:1295-305).

5. Exacerbation treatment outcomes
    a. Providers and practice will vary in defining when treatment is complete for pulmonary exacerbation. The STOP study identified the most common markers of success for providers including improvement in FEV_1 and patient-reported symptoms (J Cyst Fibros 2017;16:600-6).
    b. Though intravenous antibiotic therapy is known to improve lung function during an exacerbation, eradication of organisms in culture is neither required nor expected (Expert Opin Drug Metab Toxicol 2021;17:53-68).

C. Adjunctive therapy for prevention or treatment of pulmonary exacerbations of CF
1. Airway clearance techniques are a cornerstone of management of lung disease in CF.
    a. The type of therapy will be tailored to a patient's specific needs and preferences and the use of these interventions will likely increase during treatment of a pulmonary exacerbation (Respir Care 2009;54:522-37).
    b. High frequency chest wall oscillation, which involves an inflatable vest attached to a machine, is the most commonly used airway clearance technique (after infancy).
    c. Positive expiratory pressure/oscillating positive expiratory pressure involves breathing through a mask or mouthpiece to provide back pressure to the airways during expiration as gas also builds up behind the mucus by collateral ventilation (Cochrane Database Syst Rev 2019;11:CD003147).
    d. Despite a low level of evidence, physical exercise is recommended as a possible airway clearance therapy and is frequently used as either primary or secondary clearance for patients who are teenagers or older.
2. CFTR modulator therapy (*N Engl J Med*. 2023;389(18):1693-1707; *Eur Respir Rev*. 2024;33(173):240045; *Chest*. 2019;155(1):202-214) [re-number current options 2-5 to 3-6]
    a. It is recommended that patients with CF undergo genotyping. If patients carry a select mutation, they are eligible for CFTR modulators. CFTR modulators are oral drugs that bind to the CFTR protein and improve its function. CFTR modulators fall within 1 of 2 classes. "Potentiators" increase the probability of the CFTR protein expressed at the cell membrane, and "correctors" improve the intracellular processing of the CFTR protein.
    b. Four oral agents are FDA approved within the CFTR modulator class. All agents require dose adjustments for severe hepatic impairment or if coadministered with CYP3A4 inhibitors. With all agents, liver toxicity, elevated CK, hypertension, and cataracts should be monitored for.
        i. Elexacaftor-tezacaftor-ivacaftor: Elexacaftor 200 mg orally daily, tezacaftor 100 mg orally daily, and ivacaftor 150 mg orally every 12 hours
        ii. Ivacaftor 150 mg orally every 12 hours
        iii. Lumacaftor-ivacaftor: Lumacaftor 400 mg orally daily and ivacaftor 200 mg orally every 12 hours
        iv. Tezacaftor-ivacaftor: Tezacaftor 100 mg orally daily and ivacaftor 150 mg orally every 12 hours
    c. Abrupt withdrawal of highly active CFTR modulators should be avoided to prevent a withdrawal syndrome that has been observed (*Chest*. 2019;155(1):202-214).
    d. CFTR modulators require some dietary fat for optimal absorption, and tablets cannot be crushed for enteral administration. Ivacaftor is available as an oral granule packet that may be dissolved in liquid; however, there is no endorsement of administration through feeding tubes (*Chest*. 2019;155(1):202-214).
3. Nutrition
    a. Providing adequate nutrition according to patient-specific factors during acute exacerbations is key to maintaining metabolic function and promoting optimal outcomes.
    b. Administer pancreatic enzymes to treat exocrine dysfunction.

4. Continuation of patient's current chronic airway clearance therapy
    a. It is recommended to continue nebulized airway clearance therapies during an exacerbation (Table 2); there is limited data to describe the impact of this practice.

Table 2. Chronic Airway Clearance Therapy

Therapy	Mechanism	Clinical benefit(s)
Nebulized dornase alfa[a]	• Enzymatic cleavage of neutrophilic DNA • Reduces mucus viscosity	• Improves lung function • Improves quality of life • Reduces exacerbations
Nebulized hypertonic saline[a]	Osmotically active expectorant	
Nebulized mannitol[b]	Osmotically active expectorant	• Improves lung function

[a] Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013;187:680-9.

[b] Flume PA, Amelina E, Daines CL, et al. Efficacy and safety of inhaled dry-powder mannitol in adults with cystic fibrosis: an international, randomized controlled study. J Cyst Fibros 2021;20:1003-9.

    b. The only airway clearance therapy that has been studied specifically during pulmonary exacerbations is hypertonic saline. This study of 132 patients, randomized to either 7% hypertonic saline or control, failed to detect a difference in the primary outcome of hospital length of stay, but did find patients in the treatment group were more likely to return to baseline FEV_1 and have significantly improved symptoms at discharge (Thorax 2016;71:141-7).
5. Data remains unclear on the role of continuing patient's chronic antimicrobial regimens during an exacerbation and practice will vary.
6. The typical order of inhaled medication delivery is a bronchodilator followed by hypertonic saline, followed by chest physiotherapy, dornase alfa, and then inhaled antibiotics (*Chest*. 2019;155(1):202-214).
7. Corticosteroids
    a. Currently, there is insufficient evidence for administering corticosteroids (Am J Respir Crit Care Med 2009;180:802-8; *J Cyst Fibros*. 2020;19(3):344-354).
    b. However, current practice appears at odds with the 2009 guidelines. Though data from several small studies have been mixed, the STOP trial observed 21% of patients were treated with corticosteroids during a pulmonary exacerbation (J Cyst Fibros 2017;16:600-6).
    c. The Prednisone in Cystic Fibrosis Pulmonary Exacerbations (PIPE) trial compared 7 days of oral prednisone 1 mg/kg twice daily (maximum 60 mg per day) with placebo in patients with pulmonary exacerbation receiving intravenous antibiotics and who had not recovered to greater than 90% of their baseline FEV_1 % predicted after 7 days of antibiotics. The primary outcome was the difference in the proportion of subjects who recovered more than 90% baseline FEV_1 % predicted at day 14 of intravenous antibiotic therapy. There was no difference in FEV_1 % predicted recovery between the prednisone and placebo groups in those not responding at day 7 of intravenous antibiotic therapy. No significant differences in adverse effects were observed between groups (*Eur Respir J*. 2024;63(6):2302278).

Patient Case

Questions 1 and 2 pertain to the following case.
A 20-year-old woman is admitted to the ICU for an acute CF exacerbation. Before admission, her condition had been stable. She had maintained her ideal body weight and had just completed a home regimen of suppressive antibiotics. The patient requires MV for the management of hypoxic respiratory failure. She is initiated on AC/VC mode with a lung-protective strategy (4–8 mL/kg tidal volume).

1. Which of the following would be best to manage her acute CF exacerbation?
   - A. Tobramycin nebulization; hypertonic saline 7% nebulization; and tube feedings to target a hypocaloric goal during her acute illness (15 kcal/kg/day).
   - B. Ceftriaxone 2 g intravenously every 24 hours; tobramycin nebulization; normal saline 0.9% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).
   - C. Piperacillin/tazobactam 4.5 g intravenously every 6 hours; tobramycin 10 mg/kg intravenously once daily; hypertonic saline 7% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).
   - D. Cefepime 2 g intravenously every 8 hours extended infusion; tobramycin 10 mg/kg intravenously every 8 hours; hypertonic saline 7% nebulization; and tube feedings to target her goal caloric intake (25 kcal/kg/day).

2. After treatment with intravenous antibiotics, aggressive chest physical therapy, and her maintenance CF medications for 5 days, this patient improved and was extubated. She was moved out of the ICU on day 6 of her hospitalization. Which duration of antibiotics would be best to recommend for this patient?
   - A. 7 days.
   - B. 10 days.
   - C. 14 days.
   - D. Until cultures are negative.

II. PULMONARY ARTERY HYPERTENSION

A. Pathophysiology and Definitions

1. Pulmonary artery hypertension (PAH) is a chronic, life-threatening disease characterized by vascular changes, including vasoconstriction, cellular proliferation, and thrombosis. These changes result in elevations in pulmonary vascular resistance (PVR) with the end result being right ventricular failure.
   - a. Thromboxane A2 (potent vasoconstrictor) concentrations are increased.
   - b. Prostacyclin (potent vasodilator, inhibitor of platelet aggregation, and antiproliferative properties) concentrations are decreased.
   - c. Endothelin-1 (ET-1; potent vasoconstrictor, mitogenic properties on pulmonary artery smooth muscle cells) concentrations are increased.
   - d. Nitric oxide concentrations (vasodilator, inhibitor of platelet activation, and inhibitor of vascular smooth muscle cell proliferation) are decreased.
   - e. Cellular proliferation occurs because of downregulation of antiproliferative growth factors, which results in upregulation of the activin pathway, leading to increased vascular proliferation (*J Heart Lung Transplant.* 2024:S1053-2498(24)01874-6).

2. Clinical classification of pulmonary hypertension (PH) by group (*Eur Respir J.* 2024;64(4):2401324; *Eur Heart J.* 2022;43:3618-3731)
    a. Group 1 (PAH): Idiopathic, heritable, and drug/toxin-induced PAH, as well as PAH associated with various diseases, PAH with features of venous/capillary (PVOD/PCH) involvement, or persistent newborn PH
    b. Group 2: PH caused by left heart disease
    c. Group 3: PH caused by chronic lung disease and/or hypoxia
    d. Group 4: PH caused by chronic thromboembolic pulmonary hypertension (CTEPH) or other pulmonary artery obstructions
    e. Group 5: PH with unclear multifactorial mechanisms
3. PH is defined as a mean pulmonary artery pressure (mPAP) greater than 20 mmHg at rest as measured by right heart catheterization. *PH* is a term that encompasses all 5 groups and is not specific to any single group. (*Eur Respir J.* 2024;64(4):2401324; *Eur Heart J.* 2022;43:3618-3731)
    a. Hemodynamic definitions of PH (Eur Heart J 2022;43:3618-731; *Eur Respir J.* 2024;64(4):2401324)
        i. Groups 1, 3, 4, and 5: Precapillary PH defined as mPAP greater than 20 mmHg, pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg, and PVR greater than 2 Wood units
        ii. Group 2: Isolated postcapillary PH defined as mPAP greater than 20 mmHg, PCWP greater than 15 mm Hg, and PVR less than or equal to 2 Wood units
        iii. Group 2: Combined pre- and postcapillary PH defined as mPAP greater than 20 mmHg, PCWP greater than 15 mm Hg, and PVR greater than 2 Wood units

B. Diagnosis (Eur Heart J 2022;43:3618-731; *Eur Respir J.* 2024;64(4):2401324)
1. Initial symptoms of group 1 (PAH) are nonspecific.
    a. Common symptoms: Fatigue, shortness of breath with exertion, chest pain, and syncope
    b. Less common presentations: Dry cough, nausea, and vomiting
2. Due to the nonspecific pattern of symptoms, multiple tests will likely be needed to rule out other causes of such symptoms. This list is not complete, and additional tests may be performed based on patient-specific factors.
    a. Electrocardiogram
    b. BNP/N-terminal pro–brain natriuretic peptide (NT-proBNP)
    c. Chest radiograph
    d. Pulmonary function tests
    e. ABG
    f. Echocardiogram is used to predict likelihood of PH based on specific findings
        i. Peak tricuspid regurgitation velocity (pTRV) is a key factor in suggesting the probability of PH, but it is only a suggestive factor and should not be used independently to predict PH. Guidelines differ in their recommendation for threshold of pTRV to suggest PH, with newer guidelines using > 2.8 m/second.
        ii. Various measurements in the ventricles, pulmonary artery, inferior vena cava, and right atrium contribute to the determination of PH diagnosis.
        iii. Echocardiogram should not be used independently to diagnose PH.
    g. Ventilation/perfusion scan can be used to identify possible group 4 PH (CTEPH).
    h. Computed tomography (CT) or CT pulmonary angiography (if CTEPH is suspected)
    i. Cardiac magnetic resonance imaging can provide noninvasive prognostic assessment of the right heart initially and at follow up.
    j. Right heart catheterization is required to confirm diagnosis.
    k. Perform vasoreactivity testing if appropriate.

C. Risk Stratification of PAH (group 1 PH) (*Eur Respir J.* 2024;64(4):2401324; *Eur Heart J.* 2022;43:3618-3731)

1. PAH risk stratification is a multiparametric risk assessment tool approach that is recommended for quantifying the severity of disease, predicting patient outcomes, and guiding the treatment of PAH. The most predictive prognostic factors are 3 noninvasive parameters (WHO functional class [Table 3], 6MWD, and natriuretic peptides) that are included in all currently validated risk stratification tools.
   a. The European Society of Cardiology/European Respiratory Society (ECS/ERS) and REVEAL methods are the 2 risk stratification models recommended by guidelines. Each model stratifies a patient at diagnosis as low-, intermediate-, or high-risk status. On reassessment, a 4-stratification system is used: low-, intermediate-low, intermediate-high, or high-risk status. Risk categories are associated with 1-year mortality rates.
   b. The ECS/ERS 3-strata (Table 4) or REVEAL 2.0 models are recommended to be used at diagnosis at baseline.
   c. The ECS/ERS 4-strata (Table 5) or REVEAL Lite models are recommended to be used at 3- to 4-month intervals to assess a patient's response to therapy.

Table 3. WHO Functional Class Assessment[a]

Class	**Definition**
I	No symptoms (dyspnea, fatigue, syncope, chest pain) with normal activities
II	Symptoms with strenuous normal daily activities that slightly limit functional status and activity level; no symptoms at rest
III	Symptoms of dyspnea, fatigue, syncope, and chest pain with normal daily activities that severely limit functional status and activity level; no symptoms at rest
IV	Symptoms at rest; cannot perform normal daily activities without symptoms

[a]Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.

Table 4. Three-Strata Risk Assessment for Patients with Pulmonary Artery Hypertension at Diagnosis

Multivariable Assessment of Mortality Risk to Guide Initial Therapy			
Assessment	**3-Risk Strata**		
Estimation of 1-year mortality	**Low Risk < 5%**	**Intermediate Risk 5%–20%**	**High Risk > 20%**
Points assigned per variable[a]	1 point	2 points	3 points
Signs of right heart failure	No	No	Yes
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional during strenuous exercise	Repeated with little or normal physical activity
WHO-FC	I, II	III	IV
6-Minute walk distance	> 440 m	165–440 m	< 165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 mL/min/kg (> 65% predicted) VE/VCO_2 slope < 36	Peak VO_2 11–15 mL/min/kg (35%–65% predicted) VE/VCO_2 slope 36–44	Peak VO_2 < 11 mL/min/kg (< 35% predicted) VE/VCO_2 slope > 44

Table 4. Three-Strata Risk Assessment for Patients with Pulmonary Artery Hypertension at Diagnosis *(Con't)*

Multivariable Assessment of Mortality Risk to Guide Initial Therapy			
Assessment	**3-Risk Strata**		
BNP or NT-proBNP	BNP < 50 ng/L NT-proBNP < 300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	NP > 800 ng/L NT-proBNP > 1100 ng/L
Echocardiography parameters	RA area < 18 cm^2 TAPSE/sPAP > 0.32 mm/mm Hg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area > 26 cm^2 TAPSE/sPAP < 0.19 mm/mm Hg Moderate/large pericardial effusion
Cardiac magnetic resonance imaging	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF < 37% SVI < 26 mL/m^2 RVESVI > 54 mL/m^2
Hemodynamics	RAP < 8 mm Hg CI ≥ 2.5 L/min/m^2 SVI > 38 mL/m^2 SvO$_2$ > 65%	RAP 8–14 mm Hg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO$_2$ 60–65%	RAP >14 mm Hg CI < 2.0 L/min/m^2 SVI < 31 mL/m^2 SvO$_2$ < 60%

[a] To determine risk category, each variable available is categorized a point value as 1 point (low risk), 2 points (intermediate risk), or 3 points (high risk). The total score is added and divided by the number of variables assessed. Patients are classified as having low-, intermediate, or high-risk disease if their scores are < 1.5, 1.5-2.49, or > 2.49, respectively.

BNP, B-type natriuretic peptide; CI, cardiac index; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; SvO$_2$, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO$_2$, ventilatory equivalents for carbon dioxide; VO$_2$, oxygen uptake; WHO-FC, World Health Organization functional class.

Adapted from Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.

Table 5. Four-Strata Risk Assessment For Patients With Pulmonary Artery Hypertension

Multivariable Assessment of Mortality Risk to Guide Follow-Up Therapy				
Assessment	**4-Risk Strata**			
Prognostic determinants	**Low**	**Intermediate/Low**	**Intermediate/High**	**High**
Points[a]	1	2	3	4
WHO-FC	I or II	—	III	IV
6-Minute walk distance	> 440 m	320–440 m	165–319 m	< 165 m
BNP or NT-proBNP	< 50 ng/L < 300 ng/L	50–199 ng/L 300–649 ng/L	200–800 ng/L 650–1100 ng/L	> 800 ng/L > 1100 ng/L

[a] Divide the sum of all points by the number of variables and round to the next whole number.

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.

Adapted from Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.

2. Treatment goals for PH
   a. The goal of pharmacotherapy is to achieve and maintain a low-risk status on the recommended stratification model.
3. Supportive therapy
   a. Physical activity and rehabilitation under the direction of a PH provider for patients in stable condition may improve quality of life and 6MWD
   b. Oxygen: Maintain SaO_2 of 92% or greater and PaO_2 of 60 mm Hg or greater.

- c. Diuretics should be used for the symptomatic management of RV dysfunction and signs of fluid overload; choice of diuretic is variable.
- d. Digoxin increases cardiac output; consider in patients who develop atrial tachyarrhythmias although data specifically in PAH are not available.
- e. Anticoagulation is not generally recommended for patients with PAH and has been shown harmful in patients with PAH associated with systemic sclerosis. Consider on an individualized basis if appropriate.
- f. Aggressive treatment of sleep apnea and hypertension
- g. Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, angiotensin-receptor/neprilysin inhibitors, sodium-glucose cotransporter-2 inhibitors, β-blockers, or ivabradine are not recommended in patients with PAH unless indicated for a different comorbidity.
- h. Treatment of iron deficiency anemia is indicated, defined by serum ferritin less than 100 mcg/L, or serum ferritin 100–299 mcg/L, and transferrin saturation less than 20%.
- i. Patients with PAH should be vaccinated against influenza, *Streptococcus pneumoniae* and SARS-CoV-2 at minimum.
- j. Psychosocial support in the form of patient support groups and mental health professionals. Pharmacists play a role in disease state and pharmacotherapy education to keep patients on treatment.

4. Special populations
    - a. Pregnancy
        - i. Despite advances in treatment and management, for patients with PAH who become pregnant, birthing parent and neonatal mortality rates are high.
        - ii. People of childbearing potential should be provided with clear contraceptive recommendations. Some oral contraceptives have significant drug–drug interactions with PAH therapy, which should be considered and discussed with the patient.
    - b. Surgery
        - i. Surgical procedures pose a risk for patients with PAH. Risk increases with severity of PAH.
        - ii. Decisions to perform surgery should be made by a multidisciplinary team familiar with the risks and benefits of both the procedure and PAH.

D. Specific treatment options for group 1 PAH

1. Vasodilator therapy with calcium channel blockers (CCBs) (diltiazem, amlodipine, nifedipine)
    - a. Patients who should undergo vasoreactivity testing include those with idiopathic PAH, heritable PAH, and PAH secondary to toxins or drugs who have a cardiac index above 2 L/min/m^2 on right heart catheterization.
    - b. Considered first-line treatment for patients who have a positive response to acute vasoreactivity testing (reduced mPAP by 10 mm Hg or more to an mPAP of 40 mm Hg or less with increased or unchanged cardiac output) (N Engl J Med 1992;327:76-81)
    - c. CCBs improve mPAP, PVR, WHO FC, and survival in patients with PAH and a positive vasoreactivity test (Circulation 1987;76:135-41; N Engl J Med 1992;327:76-81). CCBs are initiated at low doses and rapidly titrated to the maximum tolerated dose.
    - d. Patients are not considered candidates for CCB therapy if they have RV dysfunction, depressed cardiac output, or WHO FC IV symptoms.
    - e. *Marked hemodynamic improvement* in patients on CCB therapy is defined as mPAP greater than 30 mm Hg and a PVR less than 4 Wood units. If patients do not reach this threshold of response, CCB therapy can be continued or stopped according to patient-specific factors; some patients may experience deterioration when CCBs are withdrawn.

2. Treatment-naïve patients with PAH (nonresponders to vasoreactivity testing) with a PVR greater than 3 Wood units and an mPAP greater than 25 mm Hg. Although the definition of PAH now includes those with an mPAP of 20 to 25 mm Hg and a PVR of 2 to 3 Wood units, these populations have not been included in clinical trials to date assessing PAH pharmacotherapies and remain an area for future research.
   a. Drug therapy should be evaluated on the basis of the patient-specific factors below (*Eur Respir J.* 2024;64(4):2401324; Eur Heart J 2022;43:3618-731):
      i. Mortality risk assessment using the 3-strata model (low, intermediate, high), as shown in Table 4
         (a) To determine risk category, each variable available is categorized a point value as 1 point (low risk), 2 points (Intermediate risk), or 3 points (high risk). The total score is added and divided by the number of variables assessed. Patients are classified as having low-, intermediate-, or high-risk disease if their scores are less than 1.5, 1.5 to 2.49, or more than 2.49, respectively (*Eur Respir J.* 2024;64(4):2401323).
      ii. Presence of cardiopulmonary comorbidities that are associated with increased risk of LV diastolic dysfunction (obesity, hypertension, diabetes, coronary heart disease)
      iii. Ability and willingness to manage parenteral prostacyclins
      iv. Access to resources
   b. Initial therapy in patients without cardiopulmonary comorbidities
      i. Low- or intermediate-risk strata (Table 4): combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i)
         (a) Recommended combinations are tadalafil and ambrisentan or tadalafil and macitentan (*N Engl J Med.* 2015;373:834-844; *Am Coll Cardiol.* 2024;83(4):473-484).
      ii. High-risk strata: combination therapy with ERA, PDE5i, and parenteral prostacyclin
   c. Initial and subsequent therapy in patients with cardiopulmonary comorbidities: because these patients are under-represented in clinical studies, no evidence-based recommendations can be provided. Although these patients are often treated similarly in practice, they have more treatment-related adverse effects or tolerability issues with combination therapy.
      i. All risk strata: oral monotherapy with PDE5i or ERA
      ii. Follow-up therapeutic changes should be based on patient-specific characteristics
3. Subsequent therapeutic options are based on the four strata risk assessment (Table 5). All 3 variables are recommended to be included in each follow-up assessment for better accuracy at predicting mortality. If only 2 variables are available, it is preferred to include 1 biomarker (BNP or NT-proBNP) and 1 functional marker (either WHO-FC or 6MWD). To determine risk category, each variable available is categorized a point value as 1 point (low risk), 2 points (intermediate-low risk), 3 points (Intermediate-high risk), or 4 points (high risk). The total score is added and divided by the number of variables assessed. Patients are classified as having low-, intermediate-low, intermediate-high, or high-risk disease if their scores are less than 1.5, 1.5 to 2.49, 2.5 to 3.49, or more than 3.49, respectively (*Eur Respir J.* 2024;64(4):2401323; *Eur Respir J.* 2024;64(4):2401324; *Am J Respir Crit Care Med.* 2024;210(5):581-592).
   a. Low-risk strata: Continue current therapy
   b. Intermediate/Low-risk strata
      i. Add an oral or inhaled prostacyclin receptor agonist (PRA)—or—
      ii. Switch from PDE5i to soluble guanylate cyclase stimulator (sGC)—or—
      iii. Add an activin-signaling inhibitor (*N Engl J Med.* 2023;388(16):1478-1490).

- c. Intermediate/High- strata
  - i. Add a parenteral prostacyclin—or—
  - ii. Add an activin-signaling inhibitor (*N Engl J Med*. 2023;388(16):1478-1490).
- d. High-risk strata
  - i. Add a parenteral prostacyclin agent (first choice if not already receiving)—or—
  - ii. Add an activin-signaling inhibitor.
- e. Persistent intermediate-high or high-risk
  - i. Refer for lung transplantation if on maximal drug therapy with: parenteral prostacyclin agent, endothelin receptor antagonist (ERA), PDE5i, sGC, activin-signaling inhibitor

E. Drug Information by Class

1. ERAs (Table 6)
   - a. Competitively block the action of ET-1 from acting on two types of ET receptors: ET_a and ET_b. This blockade prevents endogenous ET-1 from its normal actions:
     - i. ET_a = vasoconstriction and cell proliferation
     - ii. ET_b = vasodilation and antiproliferation of pulmonary endothelial cells
   - b. Minimal place in therapy for initiation in critically ill patients

Table 6. Endothelin Receptor Antagonists (oral)

	Bosentan	Ambrisentan	Macitentan
Receptor affinity	Blocks ET_a and ET_b	Preferentially blocks ET_a	Blocks ET_a and ET_b
Half-life (hr)	5	9	16
Approved dose	62.5–125 mg BID	5–10 mg daily	10 mg daily
Adverse effects	Hepatotoxicity (bosentan only), peripheral edema, anemia, contraindicated during pregnancy (As of April 4, 2025, Bosentan is the only ERA with a REMS programs)		
Drug interactions	Glyburide (contraindicated) and cyclosporine (contraindicated), CYP2C9 and CYP3A4 inhibitors and inducers, hormonal contraceptives, warfarin, sildenafil and tadalafil	Caution with cyclosporine (max ambrisentan dose is 5 mg daily)	CYP2C19 and strong CYP3A4 inhibitors and inducers

BID = twice daily; ET = endothelin; REMS = risk evaluation and mitigation strategies.

Information from: Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44; Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.

2. PDE-5 inhibitors (Table 7)
   - a. Inhibit PDE-5, which prevents the breakdown of cyclic guanosine monophosphate in pulmonary vascular smooth muscle. Increased cyclic guanosine monophosphate potentiates pulmonary vascular smooth muscle and vasodilation of the pulmonary vascular bed.
   - b. Intravenous formulation of sildenafil is available for patients who temporarily cannot ingest tablets; however, this formulation is limited by its hemodynamic effects.

Table 7. PDE5i

	Sildenafil (Revatio, Liqrev)	Sildenafil (Revatio)	Tadalafil (Adcirca, Alyq, Tadliq)
Half-life (hr)	4		35
Approved dose	20 mg oral TID	10 mg IV TID	40 mg oral daily; dose adjustment necessary for renal impairment
Adverse effects	Headache, epistaxis, flushing, dyspepsia, hypotension, visual alterations		
Drug interactions	Contraindicated in patients receiving nitrates; avoid with strong CYP3A4 inhibitors and inducers; contraindicated with riociguat		

[a]Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Chest 2019;155:565-86.

[b]Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834-44.

IV = intravenously; TID = three times daily; WHO-FC = World Health Organization functional class; 6MWD = 6-min walk distance.

3. Soluble guanylate cyclase stimulators
   a. Riociguat exerts its effect through two mechanisms: Sensitizes endogenous soluble guanylate cyclase by stabilizing nitric oxide–soluble guanylate cyclase bonding and directly stimulates soluble guanylate cyclase through an auxiliary binding site. Both processes increase cyclic guanosine monophosphate, which influences vascular tone, proliferation, fibrosis, and inflammation.
   b. For patients on ERA/PDE5i therapy and at low-intermediate risk of death, switching from PDE5i to riociguat could be considered (Lancet Respir Med 2021:9:573-84).
   c. Elimination half-life is 12 hours. If cannot be administered for 3 days or more, retitration is required; however, a PH specialist should always be involved for issues with access and reinitiation.
   d. Approved dose is 1–2.5 mg three times daily (higher doses for smokers). In patients at risk of systemic hypotension, a starting dose of 0.5 mg three times daily may be used (2022 guidelines)
   e. Adverse effects include hypotension, hemoptysis, headache, dizziness, dyspepsia, nausea, diarrhea, vomiting, and anemia.
   f. Contraindicated in patients receiving nitrates and phosphodiesterase inhibitors because of hypotension; avoid with strong CYP3A4/2C8 inhibitors and inducers and with P-glycoprotein/breast cancer resistance protein inhibitors
   g. Riociguat risk evaluation and mitigation strategies (REMS) program for embryo-fetal toxicity
4. Prostacyclins
   a. Parenteral prostacyclins (Table 8)
      i. Mimic the actions of PGI_2 (endogenous prostacyclin): Direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and antiproliferative effects
      ii. Continuous-infusion epoprostenol is the most thoroughly studied medication approved for treating PAH and has been shown to prolong survival.
         - 100% survival with intravenous epoprostenol compared with 80% survival with conventional therapies at 12 weeks (p=0.003) (N Engl J Med 1996;334:296-301)
         - 88% survival with intravenous epoprostenol compared with 59% expected survival in data from historical controls at 1 year (p<0.001) (Circulation 2002;106:1477-82)
         - 55% survival with intravenous epoprostenol compared with 28% survival in historical controls at 5 years (p<0.0001) (J Am Coll Cardiol 2002;40:780-8)
      iii. Complications related to delivery include the need for a dedicated intravenous line, local catheter/bloodstream infections, and catheter-related thrombosis.
   b. Inhaled prostacyclins (Table 8) – Advantage over intravenous route because of selective pulmonary vasodilation with minimal systemic effects

Table 8. Prostacyclins

	Epoprostenol		Treprostinil	Treprostinil	Iloprost	Treprostinil
Brand name	**Flolan**	**Veletri**	**Remodulin**	**Tyvaso**	**Ventavis**	**Orenitram**
Route of administration	IV		SC and IV	Inhalation	Inhalation	Oral
Initial dose	1–4 ng/kg/min IV		1.25 ng/kg/min IV or SC; dose adjustments in hepatic impairment	18 mcg four times daily (solution) 16 mcg four times daily (dry powder)	2.5–5 mcg six to nine times daily	0.25 mg every 12 hr or 0.125 mg every 8 hr; caution with strong CYP2C8 inhibitors and severe; contraindicated in severe hepatic impairment
Half-life	6 min		4 hr		25 min	4 hr
Adverse effects	Flushing, headache, diarrhea nausea/ vomiting, jaw pain, thrombocytopenia			Cough, throat irritation, bronchospasm, hypotension		Headache, diarrhea, nausea, flushing, jaw pain, and abdominal discomfort
Cautions	Rebound PH with abrupt discontinuation; dosing weight should not be changed without consultation with PH specialist					

CYP = cytochrome P450; IV = intravenous; PH = pulmonary hypertension; SC = subcutaneous.

Information from: Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.

c. Oral treprostinil (Table 8):
    i. The addition of oral tresprostinil to ERA or PDE5i/riociguat monotherapy is recommended to reduce the risk of morbidity and mortality in patients with idiopathic, heritable, or drug-associated PAH (Eur Heart J 2022;43:3618-731).

5. Selective prostacyclin receptor (IP receptor) agonist
    a. Selexipag is an oral and intravenous nonprostanoid that targets the prostacyclin pathway. The oral formulation cannot be crushed. An intravenous formulation has been approved for short-term use in these scenarios (*Respir Res*. 2021;22(1):34). The selexipag dose is administered twice daily and can be converted from oral by multiplying the oral dose by 1.125 (eg, selexipag 1600 μg orally twice daily is converted to selexipag 1800 μg intravenous piggyback twice daily).
    b. The 2022 ESC/ERS guidelines support
        i. Consider the addition of selexipag to ERA/PDE5i therapy for patients who present with low/intermediate risk of death at follow-up
        ii. Add selexipag if unable to use a parenteral prostacyclin for patients at intermediate/high or high risk.
        iii. Add selexipag to ERAs and/or PDE5is to reduce the risk of clinical deterioration.
    c. It is not recommended to start macitentan, tadalafil, and selexipag as initial therapy, given the lack of current evidence for this strategy (J Am Coll Cardiol 2021;78:1393-403).
    d. Elimination half-life is 0.8–3 hours and, for the active metabolite, 6–14 hours. If unable to administer for 3 days or more, retitration is required; however, a PH specialist should always be involved for issues with access and reinitiation.
        i. If oral selexipag therapy is being held because of lack of ability to administer enterally, it can be converted to the intravenous formulation temporarily while hospitalized.

   e. Approved dose is 200 mcg twice daily; increase at weekly intervals to the highest tolerated dose (maximum dose 1600 mcg twice daily); adjustment necessary for moderate hepatic impairment
   f. Dosing should be reduced to once daily in patients receiving moderate CYP2C8 inhibitors whereas selexipag is contraindicated in patients receiving strong CYP2C8 inhibitors (e.g., gemfibrozil); dose increase necessary with CYP2C8 inducers
   g. Adverse effects include headache, diarrhea, nausea and jaw pain.

6. Activin-signaling inhibitor
   a. Sotatercept is a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein that binds to activin A to improve the balance between pro-proliferative and antiproliferative signaling to modulate vascular proliferation (*J Heart Lung Transplant.* 2024:S1053-2498(24)01874-6).
   b. The 7th World PH Symposium recommendations for use of sotatercept include using it as add-on therapy for those receiving ERA/PDE5i combination therapy at intermediate-low, intermediate-high, and high risk (in those already receiving parenteral prostacyclin) (*Eur Respir J.* 2024;64(4):2401325).
   c. Sotatercept is a subcutaneous injection that is administered every 3 weeks. The initial dose is 0.3 mg/kg subcutaneously × 1 dose, followed by 0.7 mg/kg subcutaneously every 3 weeks.
      i. The half-life is around 24 days.
      ii. Unlike other PAH medications, sotatercept does not provide an acute pulmonary vasodilatory activity, thus potentially limiting its role in the critically ill population (*J Cardiovasc Pharmacol Ther.* 2024;29:10742484231225310).
   d. Adverse events include bleeding events (eg, epistaxis), headache, diarrhea, telangiectasia, dizziness, thrombocytopenia, increased hemoglobin, and hypertension.
      i. Baseline hemoglobin and platelets are required before initiating therapy. Repeat hemoglobin and platelets are required before the first 5 doses. If the platelets decrease to less than 50 × 103/μL or the hemoglobin increases to greater than 2 g/dL from the previous dose and is above the upper limit of normal (ULN), increases greater than 4 g/dL from baseline, or is greater than 2 g/dL above the ULN, it is recommended to delay treatment by 3 weeks. Hemoglobin and/or platelets should be reassessed before resuming sotatercept. If treatment is delayed greater than 9 weeks, the sotatercept dose should be modified to 0.3 mg/kg subcutaneously × 1 dose, followed by 0.7 mg/kg subcutaneously every 3 weeks.

F. Managing Decompensated PAH

1. Decompensated PAH generally presents with worsening symptoms of right heart failure such as shortness of breath, syncope, fluid retention, or even multiorgan failure due to poor perfusion (*Eur Respir J.* 2019;53:1801906).
2. Markers of imminent mortality from PAH/severe right sided heart failure include a decline in central venous oxygen saturation, lactic acidosis, and decreased urine output.
3. Manage contributing factors such as infections, anemia, arrhythmias, rebound PH (nonadherence or ineffective dosing), hypoxemia, acidosis, and metabolic abnormalities. Because of the hemodynamic effects of MV, both invasive and noninvasive, it is recommended to correct hypoxia using high-flow nasal cannula. Application of MV and PEEP increases PVR. It is recommended to use MV only if high-flow nasal cannula does not correct hypoxia (*Crit Care Clin.* 2024;40(1):121-135).
4. Supportive therapies include optimizing RV preload through fluid optimization (diuretics or dialysis), maintaining aortic root pressure, improving RV contractility, and reducing RV afterload.
5. Temporary discontinuation of CCBs and β-blockers to eliminate negative inotropic effects
6. Hemodynamic support (Table 9)
   a. Maintaining aortic root pressure and minimizing RV ischemia can be accomplished using vasopressors, which increase the systemic vascular resistance (SVR) and ultimately improve RV perfusion (Crit Care Med 2007;35:2037-50).

b. Direct effects on the pulmonary circulation from vasopressors may increase the PVR, potentially leading to further clinical decompensation.

c. Few studies have been published to help guide selection of the optimal vasopressor in patients with PH; recommendations are extrapolations from other patient populations.
   i. Experts recommend norepinephrine as the vasopressor of choice in decompensated PAH in patients with low SVR because of its neutral impact on PVR at lower doses (less than 0.5 µg/kg/min) and reduced arrhythmogenic potential compared with dopamine (*Heart Fail Rev.* 2016;21(3):323-346; *Eur Respir J.* 2019;53(1):1801906).
   ii. Vasopressin can be considered as a first-line option or as an add-on to norepinephrine at physiologic dosing (up to 0.03-0.04 units/min) in low SVR states because of its neutral effects on PVR and ability to reduce norepinephrine requirements that may lead to the increased PVR that can be seen with high doses (*Heart Fail Rev.* 2016;21(3):323-346; *Eur Respir J.* 2019;53(1):1801906).
   iii. Dopamine and epinephrine are second-line options because of the high risk of arrhythmia relative to norepinephrine (*Heart Fail Rev.* 2016;21(3):323-346; *Eur Respir J.* 2019;53(1):1801906).
   iv. Phenylephrine should be avoided because of its isolated α_1 activity that leads to unopposed increases in PVR without augmentation of cardiac function (*Heart Fail Rev.* 2016;21(3):323-346; *Eur Respir J.* 2019;53(1):1801906).

d. Inotropes are used to further augment the cardiac output of the RV and may improve PVR. Because of systemic vasodilatory properties from inotropes, expect possible systemic hypotension and need for vasopressors.

Table 9. Agents Used for Hemodynamic Support for Decompensated PH

Drug	Site of Action (receptor activity)	Effects on PVR	Effects on CO	Comments
Dopamine	Dose-dependent dopaminergic, α_1 and β_1	↑	↑	May not improve RV ejection fraction; arrhythmias
Norepinephrine[a]	$\alpha_1 > \beta_1$	↑ or ↔	↑	Decreased mortality in subgroup of cardiogenic shock and decreased rate of arrhythmias compared with dopamine in a randomized trial
Phenylephrine	α_1	↑	↔	Reflex bradycardia may be harmful in the setting of RV failure
Epinephrine	$\alpha_1, \beta_1 > \beta_2$	↑ or ↔	↑	Arrhythmias, hyperglycemia, increased lactate concentrations
Vasopressin	V_1 receptors	↔	↑ or ↔	Use low dose (≤ 0.03 units/min)
Dobutamine	$\beta_1 > \beta_2$	↓	↑	Combine with peripheral vasoconstrictor to attenuate systemic vasodilation
Milrinone	PDE-3 inhibitor	↓	↑	Combine with peripheral vasoconstrictor to attenuate systemic vasodilation

Information from Hoeper 2019.

CO = cardiac output; PDE-3 = phosphodiesterase-3; PVR = pulmonary vascular resistance; RV = right ventricular.

7. Unloading the RV with pulmonary vasodilators is essential to controlling decompensated PH and RV failure.
   a. In select scenarios, temporary inhaled epoprostenol or inhaled nitric oxide may be considered in those who are too unstable to tolerate the systemic blood pressure effects of PAH therapies. These inhaled options have been described in the literature administered by invasive MV, high-flow nasal cannula, and noninvasive MV (*Crit Care.* 2014;18(5):524; *Crit Care.* 2014;18(5):523; *Ann Pharmacother.* 2018;52(12):1173-1181). A protocolized approach should be used for inhaled epoprostenol, given the complexity of the administration method. Initial doses described in the literature for inhaled epoprostenol include 0.01 to 0.05 μg/kg/min, and for nitric oxide, the range described is 5 to 20 ppm (*Ann Pharmacother.* 2013;47(6):790-796).
   b. Patients admitted to the ICU for PAH compensation are generally candidates for escalation in disease-targeted medications. These patients typically meet the criteria for intermediate-high or high-risk classification. When clinically appropriate (eg, hemodynamically stable, able to tolerate medications by mouth), escalation of therapy is warranted in conjunction with a PAH specialist.
   c. All PAH medications, except for PDE5i, are specialty medications. The process to assess for patient access to therapy once stable for discharge should be initiated once the patient has been stabilized.
8. If a patient is not responsive to therapy and may be a transplant candidate, extracorporeal life support can be considered as a bridge to lung transplant. Candidates must be chosen prudently because RV failure must be reversible for this strategy to be successful.

Patient Case

Questions 3 and 4 pertain to the following case.
A 44-year-old man is transferred to the medical ICU for treatment of his worsening PAH. He currently receives no PAH treatment. The patient has had increased dyspnea on exertion for the past 6 months with exercise. For the past 2 months, he has had difficulty going for walks with his dog without getting fatigued, and occasionally, he has chest pain. In the past few days, he has had severe shortness of breath at rest, which prompted him to come to the hospital. His physical examination is remarkable for blood pressure 105/64 mm Hg and heart rate 85 beats/minute. Lung examination is clear, and extremities are notable for trace edema. An echocardiogram reveals an elevated pulmonary systolic pressure and a normal ejection fraction. The patient has an unfavorable response to vasodilator challenge. Pertinent laboratory data are serum urea nitrogen 10 mg/dL, SCr 0.6 mg/dL, AST 160 U/L, and ALT 100 U/L.

3. Which best describes his WHO FC and risk of mortality in the next year?
   A. WHO FC III, mortality risk 5%.
   B. WHO FC III, mortality risk 10%.
   C. WHO FC IV, mortality risk 15%.
   D. WHO FC IV, mortality risk greater than 20%.

4. Which medication therapy would be best to recommend initiating at this time?
   A. Epoprostenol infusion at 2 ng/kg/minute.
   B. Diltiazem 180 mg orally daily.
   C. Macitentan 10 mg orally daily.
   D. Sildenafil 10 mg intravenously three times daily.

III. ASTHMA EXACERBATION

A. Pathophysiology and Classification of Exacerbations (Global Initiative for Asthma 2024)

1. Asthma is a heterogeneous disease, usually categorized by chronic airway inflammation. It is defined by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, together with variable expiratory airflow limitations.
2. Asthma exacerbations are, also termed *acute severe asthma*, characterized by decreases in expiratory airflow from the patient's usual state that can be quantified by spirometry or peak expiratory flow.
3. Definitions and classifications of asthma exacerbations vary between experts and guidelines. Both terms below are considered life threatening exacerbations.
    a. Status asthmaticus is an acute severe asthma exacerbation that does not respond to initial intensive therapy, with the potential for pulmonary compromise and death.
    b. Near-fatal asthma is status asthmaticus that progresses to respiratory failure.

Table 10. Classification of Asthma Exacerbations in Acute Care Facility (Global Initiative for Asthma 2024)

	Symptoms	**Initial PEF (or FEV$_1$)**	**Clinical Course**
Mild/ Moderate	• Talks in phrases • Prefers sitting to laying down • Not agitated • RR increased • Accessory muscles not used • Heart rate 100–120 beats/min • Sao$_2$ 90%–95%	> 50% of predicted or personal best	• Usually cared for at home/primary care setting • Relief from frequent inhaled SABA • Consider addition of ipratropium • Recommended course of oral CS • Sao$_2$ goal 93%–95%
Severe	• Talks in words • Sits hunched forward • Agitated • RR > 30 breaths/min • Accessory muscles used • Heart rate > 120 beats/min • Sao$_2$ < 90%	≤ 50% of predicted or personal best	• Requires ED visit and likely hospitalization • Recommended inhaled SABA + ipratropium bromide • Sao$_2$ goal 93%–95% • Oral or IV corticosteroids • Consider IV magnesium • Consider high dose ICS
Life threatening	• Drowsy • Confused • Silent chest (absent breath sounds)	No definition	• Requires hospitalization; possible ICU admission; assess patient for intubation • Minimal or no relief from frequent inhaled SABA • IV corticosteroids • Adjunctive therapies are helpful

ED = emergency department; FEV$_1$ = forced expiratory volume in the first second of expiration; ICS = inhaled corticosteroid; ICU = intensive care unit; IV = intravenous; PEF = peak expiratory flow; RR = respiratory rate; SABA = short-acting β-agonist; Sao$_2$ = oxygen saturation.

Adapted from: Global Initiative for Asthma 2024.

B. Common Causes of Asthma Exacerbations (Global Initiative for Asthma 2024)

1. Viral infections
2. Allergen exposure
3. Food allergy
4. Air pollution

5. Seasonal weather changes
6. Poor adherence to inhaled corticosteroids

C. Mortality Risk Factors (*Multidiscip Respir Med.* 2016;11:37; Global Initiative for Asthma 2024)
   1. History of near-fatal asthma (e.g., requiring MV)
   2. Hospitalization or ED visit for asthma in the past year
   3. Active use of oral corticosteroids or completion of recent course for asthma
   4. Not currently using inhaled corticosteroids
   5. Use of more than one canister of short-acting β-agonists (SABAs) per month
   6. Poor adherence to inhaled corticosteroid containing asthma medications and/or poor adherence to asthma action plan
   7. History of psychiatric disease or psychosocial problems
   8. Food allergy in a patient with asthma
   9. Social history that includes major psychosocial problems or psychiatric illness
   10. Food allergies
   11. Comorbidities including pneumonia, diabetes, and arrhythmias

D. Social Determinants of Health in patients with asthma (Ann Allergy Asthma Immunol 2022;128:5-11)
   1. Black and Latinx Americans have higher asthma prevalence and asthma-related morbidity than other populations.
   2. Adults with a household income < $50,000 had a 1.6 times higher rate of asthma treatment failure and 2 times higher rate of asthma exacerbations compared with those with a household income >=$50,000.
   3. The impacts of long-term stress, health care access, environmental factors, education level, and food accessibility on disease prevalence and management in patients with asthma are active areas of research.

E. COVID-19 (SARS-CoV-2) and Asthma (GINA 2024)
   1. Patients with well-controlled asthma do not appear to be at increased risk of infection or mortality due to SARS-CoV-2.
   2. However, patients who acquire COVID-19 with poorly controlled asthma (eg, recent need of oral corticosteroids) are at higher risk of hospitalization for severe disease.
   3. Both GINA and the Centers for Disease Control and Prevention recommend that patients receive vaccination against COVID-19 including boosters if applicable.
   4. If patients are receiving biologics for their severe asthma, it is not recommended to give the first dose of a biologic agent and the COVID-19 vaccine on the same day.

F. Alternative Causes (mimic asthma exacerbation) (*N Engl J Med.* 2023;389(11):1023-1031)
   1. Upper airway: Vocal cord dysfunction, anaphylaxis, laryngeal stenosis
   2. Central airway: Tracheomalacia, tracheal stenosis mucus plugging
   3. Lower airway: Bronchiolitis, COPD, valvular heart disease, diastolic heart dysfunction

G. ABG Assessment
   1. Patients with acute severe asthma initially experience a respiratory alkalosis.
   2. As respiratory status worsens, arterial carbon dioxide increases (patient exhaustion, inadequate alveolar ventilation and/or an increase in physiologic dead space), leading to respiratory acidosis. A Pao_2 less than 60 mm Hg with or without a $Paco_2$ greater than 45 mm Hg may also indicate respiratory failure.
   3. Metabolic (lactic) acidosis may coexist. Lactate production presumably stems from the use of high-dose β-agonists, increased work of breathing resulting in anaerobic metabolism of the ventilatory muscles, and tissue hypoxia.

H. Oxygen
   1. Oxygen therapy is important in managing acute severe asthma.
   2. Oxygen by nasal cannula or mask should be administered to patients with severe exacerbations with hypoxemia to achieve Sao_2 values greater than 93%–95% (pregnant women and patients with a cardiac history may require higher goals) (GINA 2024; Thorax 2011;66:937-41).

I. High-Flow Nasal Cannula and Noninvasive Ventilation: Data are insufficient for use in severe exacerbations (Global Initiative for Asthma 2024). Recent data indicate that these modalities are increasingly being used (*Ann Am Thorac Soc*. 2024;21(10):1441-1448). If attempted, patients should not be sedated to tolerate noninvasive ventilation. Further research is needed to define the roles of these modalities in severe asthma exacerbation (*Can Respir J*. 2020;2020:2301712; *Am J Respir Crit Care Me*d. 2020;202(11):1520-1530).

J. Mechanical Ventilation
   1. Indications
      a. Worsening hypoxemia or hypercarbia
      b. Drowsiness or altered mental status
      c. Hemodynamic instability
      d. Increased work of breathing
   2. Low minute ventilation (by reduced tidal volume and/or respiratory rate), high inspiratory flow rate, and minimal PEEP on the ventilator will help minimize dynamic hyperinflation.

K. β-Agonists
   1. SABAs stimulate the β_2-receptors on smooth muscle cells, leading to relaxation of respiratory smooth muscle and causing bronchodilation and decreased airway obstruction.
   2. SABAs are the cornerstone in managing acute severe asthma.
   3. Patients with an asthma exacerbation should receive a SABA repeatedly by either an MDI or nebulization at presentation, and the SABA should be continued until acute symptoms have resolved (Global Initiative for Asthma 2024).
   4. Patients with acute severe exacerbations may benefit from continuous versus intermittent nebulization of SABAs, though differences in outcomes between studies are conflicting (Global Initiative for Asthma 2024; Cochrane Database Syst Rev 2003;4:CD001115).
      a. Intermittent dosing of albuterol: 2.5–5 mg every 20 minutes for three doses; then 2.5–10 mg every 1–4 hours as needed
      b. Continuous nebulization of albuterol: 10–15 mg/hour
   5. Systemic β-agonists can be considered if the patient does not respond to inhaled therapy after several hours (Chest 2022;162:747-56).
      a. These agents have no proven advantage over inhaled agents or over each other and are not recommended for routine use because of the high rate of adverse effects.
      b. However, if the patient's acute asthma exacerbation is caused by anaphylaxis or angioedema, epinephrine would be recommended.
      c. Epinephrine 1 mg/mL 0.3–0.5 mg intramuscularly/subcutaneously every 20 minutes up to three doses
      d. Epinephrine infusion 0.1 mcg/kg/minute
      e. Terbutaline 0.25 mg subcutaneously every 20 minutes for three doses
   6. Adverse effects include tremor, tachyarrhythmias, hypokalemia, tachyphylaxis, hyperglycemia, and type B lactic acidosis.

L. Anticholinergic Agents
  1. Inhaled anticholinergic agents selectively bind to the muscarinic receptors on smooth muscle cells in the airways and thereby reduce bronchoconstriction.
  2. Short-acting inhaled anticholinergic agents (ipratropium bromide) should be given in combination with a SABA in moderate to severe exacerbations to promote additional bronchodilation through a different pathway.
  3. Adding ipratropium to inhaled albuterol compared with using albuterol alone in patients with severe asthma improved the response; however, outcomes with this combination in status asthmaticus or near-fatal asthma remain elusive (Am J Respir Crit Care Med 2000;161:1862-8). Combination therapy consisting of inhaled short-acting anticholinergics and a SABA compared with a SABA alone has reduced hospitalization rates in severe asthma exacerbations. However, combination therapy may increase the risk of adverse drug events, including agitation and palpitations (Cochrane Database Syst Rev 2017;1:CD001284).
  4. Adverse effects include headache, flushed skin, blurred vision, tachycardia, palpitations, and urinary retention.

M. Corticosteroid Therapy
  1. Corticosteroids decrease airway obstruction during an asthma exacerbation by decreasing inflammation, increasing the number of β2-receptors and increasing their responsiveness to β-agonists, reducing airway edema, and suppressing certain proinflammatory cytokines (Respir Med 2004;98:275-84).
  2. Systemic corticosteroids should be administered to patients who have moderate or severe exacerbations or to patients who do not respond promptly and completely to SABA treatment (Am J Med 1983;74:845-51).
  3. Typically, there is a 6–8-hour delay in the response to corticosteroids in status asthmaticus or life threatening asthma; therefore, administration should be considered early in the course (within 1 hour of presentation) (Cochrane Database Syst Rev 2001;1:CD002178).
  4. Oral prednisone is considered as effective as parenteral corticosteroids in most patients; however, it may not be as effective in critically ill patients with impaired gastric absorption.
  5. GINA guidelines recommend prednisone 1 mg/kg/day up to a maximum of prednisone 50 mg daily for 5–7 days for treatment of exacerbations.
    a. Other guidelines recommend longer courses and higher doses for life threatening asthma exacerbations based on the same evidence used by GINA.
    b. For corticosteroid courses less than 2 weeks (GINA 2024), tapering is not necessary, especially if patients are concurrently using an inhaled corticosteroid.
  6. Inhaled corticosteroids can be initiated any time in the treatment of an asthma exacerbation. It is not recommended to replace systemic steroids with inhaled corticosteroids (Respir Care 2018;63:783-96).

N. Adjunctive Therapies (Respir Care 2018;63:783-96; J Clin Med 2019;8:1283)
  1. Ketamine is a phencyclidine derivative that has bronchodilatory properties that reduce airway resistance and prevent the reuptake of norepinephrine, which may stimulate β_2-receptors (Indian J Crit Care Med 2013;17:154-61). Ketamine may be used for as an induction for rapid sequence induction or sedation for MV (Chest 2022;162:747-56).
  2. Magnesium sulfate (2 g intravenously administered over 20–30 minutes) can be considered in patients who have life-threatening exacerbations and are unresponsive to conventional therapies after 1 hour (GINA 2024).
    a. Magnesium is thought to cause bronchodilation by inhibiting calcium channels on smooth muscle, leading to relaxation.
    b. In addition, magnesium may have anti-inflammatory properties that interfere with the activation and release of neutrophils in patients with asthma.

   c. Data for magnesium sulfate administration in severe asthma exacerbations are mixed. In addition, data exist using nebulized magnesium rather than intravenous, but evidence is currently not robust enough to recommend (Front Allergy 2023;4:1211949).

3. Centers equipped with extracorporeal membrane oxygenation may offer this as a bridge to recovery if a patient's respiratory acidosis cannot be managed by invasive MV alone (Global Initiative for Asthma 2024; *Chest*. 2023;163(1):38-51)

O. Treatments Not Recommended (GINA 2024)

1. Methylxanthines (theophylline and aminophylline) do not improve lung function or other outcomes in hospitalized adults. Use is associated with severe adverse effects.
2. Antimicrobials are not generally recommended for acute asthma exacerbations; however, they can be considered if there is evidence of concurrent infection.
3. Helium-oxygen (heliox) is a blended gas (mixture of about 70%-80% helium and 20%-30% oxygen) that decreases airway resistance, leading to improved airflow and ventilation. Evidence does not support the routine use of heliox. Use of heliox in status asthmaticus may delay the need for intubation by allowing other therapies to work or as a delivery mechanism for nebulized SABAs (Global Initiative for Asthma 2024).

Patient Case

Questions 5 and 6 pertain to the following case.
A 30-year-old woman (weight 115 kg) with status asthmaticus is admitted to the ICU. She has a history of severe refractory asthma that has required endotracheal intubation three times in the past 6 months. Her medical history includes hypertension, diabetes, obesity, and bipolar disorder. She has used at least three canisters of albuterol per month for the past 2 months to manage her symptoms.

5. Which best represents the patient's risk factors for higher mortality?
   A. Three hospitalizations in the past 6 months and bipolar disorder.
   B. Use of more than two canisters of SABAs in the past month and obesity.
   C. Hospitalization for asthma in the past month and diabetes.
   D. Prior episode of near-fatal asthma and hypertension.

6. The patient is endotracheally intubated and placed on MV. Which would be the most appropriate initial therapy for this patient with life-threatening asthma exacerbation?
   A. Inhaled albuterol by nebulization 2.5 mg every 4 hours.
   B. Inhaled albuterol by nebulization 2.5 mg every 4 hours and inhaled ipratropium by nebulization 0.5 mg every 6 hours.
   C. Inhaled albuterol by nebulization 2.5 mg every 4 hours, inhaled ipratropium by nebulization 0.5 mg every 6 hours, and methylprednisolone 40 mg intravenously daily.
   D. Inhaled albuterol by nebulization 2.5 mg every 4 hours, inhaled ipratropium by nebulization 0.5 mg every 6 hours, and methylprednisolone 125 mg intravenously every 6 hours.

IV. ACUTE CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATION

A. Chronic Obstructive Pulmonary Disease (COPD) (GOLD 2024)

1. COPD is defined as a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, exacerbations) as a result of abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction (Table 11).

Table 11. Classification of Airflow Limitation Severity in Chronic Obstructive Pulmonary Disease

Grade	Spirometric GOLD Classification (based on post-bronchodilator FEV$_1$)
GOLD 1: Mild	FEV$_1$ $\geq$ 80% predicted
GOLD 2: Moderate	50% $\leq$ FEV$_1$ < 80% predicted
GOLD 3: Severe	30% $\leq$ FEV$_1$ < 50% predicted
GOLD 4: Very severe	FEV$_1$ < 30% predicted

FEV$_1$ = forced expiratory volume in the first second of expiration; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

Adapted from: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD. 2024.

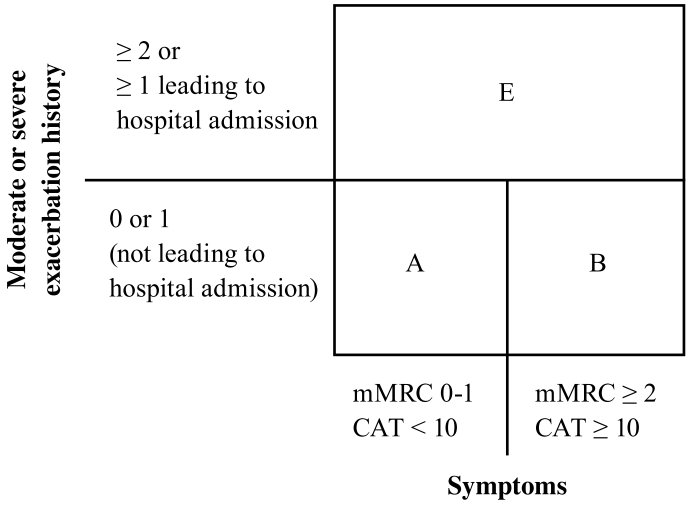
Moderate or severe exacerbation history
≥ 2 or ≥ 1 leading to hospital admission
E
0 or 1 (not leading to hospital admission)
A
B
mMRC 0-1 CAT < 10
mMRC ≥ 2 CAT ≥ 10
Symptoms

Figure 1. Assessment of Chronic Obstructive Pulmonary Disease Symptoms and Risk of Exacerbations

CAT = Chronic Obstructive Pulmonary Disease Assessment Test; mMRC = Modified British Medical Research Council Questionnaire.

2. Exacerbations of COPD (ECOPD): An event that is characterized by increased dyspnea and/or cough and sputum that worsen over less than 14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs (Am J Respir Crit Care Med 2021;204:1251-8)

3. Diagnosis of ECOPD
    a. Symptoms, severity of dyspnea using a visual analog scale, and documentation of the presence of cough should be assessed.
    b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use) should also be assessed.
    c. Severity should be evaluated with Spo$_2$, C-reactive protein (CRP), and ABG (venous blood gas to assess pH and bicarbonate is an acceptable alternative).
    d. Identify the etiology of the event (viral, bacterial, or environmental).
    e. Spirometry is not accurate during an exacerbation and is not recommended.
    f. Assess for other etiologies that may explain a patient's symptoms (ie, pneumonia, heart failure, pulmonary embolism).
4. Classifications of ECOPD

Table 12. Classification of ECOPD Severity

ECOPD Severity	Description	Diagnostic Parameters
Mild	Treated with short-acting bronchodilators only	Patient must exceed three of the listed variables to move to moderate • Dyspnea VAS < 5 • RR < 24 breaths/min • HR < 95 beats/min • Resting Spo$_2$ ≥ 92% breathing ambient air (or patient's usual oxygen prescription) AND change ≤ 3%[a] • CRP < 10 mg/L (if available)
Moderate	Treated with short-acting bronchodilators and oral corticosteroids with or without the addition of antibiotics	• Dyspnea VAS ≥ 5 • RR ≥ 24 breaths/min • HR ≥ 95 beats/min • Resting Spo$_2$ < 92% breathing ambient air (or patient's usual oxygen prescription) AND/OR change > 3%[a] • CRP ≥ 10 mg/L (if available) • If ABG obtained, hypoxemia and/or hypercapnia may be present (Pao$_2$ ≤ 60 mm Hg, Paco$_2$ > 45 mm Hg), but acidosis will be absent
Severe	Patient requires ED visit or hospitalization; patient may also experience acute respiratory failure	• Dyspnea, RR, HR, Sao$_2$, and CRP parameters identical to those for moderate severity • ABG shows new hypercapnia and acidosis (Paco$_2$ > 45 mm Hg and pH < 7.35)

[a] Pulse oximetry (Spo$_2$) is not as accurate as an ABG, and there is a risk of overestimation of blood oxygenation saturation in patients with darker skin tones (N Engl J Med 2020;383:2477-8).

ABG = arterial blood gas; CRP = C-reactive protein; ECOPD = exacerbations of chronic obstructive pulmonary disease; ED = emergency department; HR = heart rate; RR = respiratory rate; Sao$_2$ = oxygen saturation; Spo$_2$ = functional oxygen saturation; VAS = visual analog scale.

Adapted from: The ROME Proposal (Am J Respir Crit Care Med 2021;204:1251-8); GOLD guidelines 2024.

5. Definitions of ECOPD respiratory failure (GOLD 2024)

Table 13. Definitions of ECOPD Respiratory Failure

No respiratory failure	• RR ≤ 24 breaths/min • HR < 95 beats/min • No accessory respiratory muscle use • No change in mental status • Hypoxemia improved with supplemental oxygen by Venturi mask 24%–35% F_{IO_2} • No increase in Pa_{CO_2}
Acute respiratory failure – non–life threatening	• RR > 24 breaths/min • Accessory respiratory muscle use • No change in mental status • Hypoxemia improved with supplemental oxygen by Venturi mask > 35% F_{IO_2} • Hypercarbia; Pa_{CO_2} increased compared with baseline or elevated 50–60 mm Hg
Acute respiratory failure – life threatening	• RR > 24 breaths/min • Accessory respiratory muscle use • Acute changes in mental status • Hypoxemia not improved with supplemental oxygen by Venturi mask > 40% F_{IO_2} • Hypercarbia; Pa_{CO_2} increased compared with baseline or elevated > 60 mm Hg or the presence of acidosis (pH ≤ 7.25)

ECOPD = exacerbations of chronic obstructive pulmonary disease; F_{IO_2} = fraction of inspired oxygen; HR = heart rate; RR = respiratory rate.

B. Common Causes of ECOPD (Global Initiative for Asthma 2024)
  1. Respiratory tract infection (40%–50% of ECOPD)
    a. Bacterial (J Infect 2013;67:516-23)
      i. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common organisms.
      ii. *Pseudomonas aeruginosa* and other gram-negative organisms are more common in patients with frequent exacerbations (Chest 1998;113:1542-8; Chest 1999;116:40-6; Respir Med 2003;97:770-7; Chest 2007;131:44-52; Eur Respir J 2009;34:1072-8; J Infect 2013;67:516-23).
    b. Viral SARS-CoV-2, influenza, rhinovirus, parainfluenza, respiratory syncytial virus
  2. Medication nonadherence
  3. Temperature change
  4. Air pollution

C. Oxygen
  1. Oxygen therapy is important in managing ECOPD.
  2. Oxygen by nasal cannula or mask should be administered to patients with severe exacerbations to achieve an Sa_{O_2} of 88-92% (BMJ 2010;341:c5462).
  3. Caution is advised with oxygen supplementation in patients with COPD (Crit Care 2012;16:323; Global Initiative for Chronic Obstructive Lung Disease 2024):
    a. A slight level of hypoxemia may serve as a trigger for their respiratory drive secondary to chronic hypercapnia.
    b. May increase ventilation/perfusion mismatch and decrease respiratory rate centrally and perpetuate the Haldane effect
    c. A recent post hoc analysis of two prospective COPD trials suggests that exceeding an Sa_{O_2} of 92% is associated with increased mortality (HR 1.98 for Sa_{O_2} 93%–96%, HR 2.97 for Sa_{O_2} 97%–100%) (Emerg Med J 2021;38:170-7).

D. High-Flow Oxygen Therapy by Nasal Cannula
   1. Alternative to standard oxygen therapy or noninvasive positive pressure ventilation (GOLD 2024)
   2. Improves oxygenation and ventilation in patients with COPD and very severe underlying disease (Thorax 2016;71:759-61)

E. Noninvasive MV
   1. Indications for noninvasive MV include at least one of the following (GOLD 2024):
      a. Respiratory acidosis (Pa_{CO_2} 45 mm Hg or greater and/or arterial pH 7.35 or less)
      b. Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both; use of accessory muscles; paradoxical motion of the abdomen; or retraction of the intercostal spaces
      c. Persistent hypoxemia despite supplemental oxygen
   2. NIV is preferred to invasive MV as the initial management of acute respiratory failure. NIV improves gas exchange, reduces work of breathing and need for MV, decreases hospitalization duration, and improves survival (N Engl J Med 1995;333:817-22; Eur Respir J 2017;49:1600791).

F. Mechanical Ventilation: Indications for invasive MV (GOLD 2024)
   1. Unable to tolerate or failure of noninvasive MV
   2. After respiratory or cardiac arrest
   3. Altered level of consciousness
   4. Aspiration or vomiting
   5. Hemodynamic instability despite fluid and vasopressors
   6. Severe ventricular or supraventricular arrhythmias
   7. Life-threatening hypoxemia and inability to tolerate noninvasive ventilation
   8. Inability to manage respiratory secretions

G. Bronchodilators
   1. Inhaled SABAs (nebulized or MDI) with or without a short-acting anticholinergic are preferred for bronchodilation in ECOPD.
   2. Continue long-acting β-agonists and anticholinergic agents, although no studies have evaluated this regimen. If patients have not yet started these agents, initiate long-acting agents as soon as patient is stable and prior to discharge.
   3. Currently, evidence is lacking regarding a mode of delivery when comparing nebulizers with MDIs during ECOPD, though continuous nebulization is not recommended (GOLD 2024; Cochrane Database Syst Rev 2016;8:CD011826).
   4. Treatments NOT recommended: Methylxanthines (theophylline and aminophylline) because of significant adverse effects

H. Corticosteroid Therapy
   1. Corticosteroids shorten recovery time, improve lung function (FEV_1), improve oxygenation, and decrease the risk of early relapse, treatment failure, and length of hospitalization (GOLD 2024; N Engl J Med 1999;340:1941-7; Chest 2001;119:726-30). Prednisone 40 mg daily or equivalent (preferably oral) for 5 days may shorten recovery time in acute ECOPD. If oral administration is not an option, equivalent doses of intravenous methylprednisolone or nebulized budesonide can be administered (GOLD 2024).

2. Literature review
    a. Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) was a randomized, noninferiority trial. Patients (n=314) were randomized to prednisone 40 mg daily for either 5 days or 14 days (inhaled bronchodilators and antimicrobials in both groups). ECOPD occurred in 35.9% of patients in the 5-day group and in 36.8% of patients in the 14-day group (p=0.006) In addition, although one of the secondary endpoints notes no difference between groups regarding the need for mechanical ventilation (defined as either intubation or noninvasive ventilation), it is unclear how many patients in the study population were critically ill. (JAMA 2013;309:2223-31). This study did not include critically ill patients requiring MV.
    b. A randomized, double-blind trial including 83 adult patients with an ECOPD requiring hospitalization and ventilatory support (invasive or noninvasive) compared methylprednisolone 0.5 mg/kg intravenously every 6 hours for 72 hours, 0.5 mg/kg every 12 hours on days 4–6, and 0.5 mg/kg daily on days 7–10 with placebo. Patients receiving corticosteroids had a shorter duration of MV (p=0.04), trend toward shorter length of ICU stay (p=0.09), fewer noninvasive ventilation failures (p=0.004), and more hyperglycemia (p=0.04). This study was not powered to detect differences in length of stay or mortality (Arch Intern Med 2011;171:1939-46).
    c. An open-label, randomized trial included 217 critically ill patients 40 years and older with an ECOPD requiring MV to receive oral prednisone 1 mg/kg daily for a maximum of 10 days or usual care. No differences in ICU mortality, noninvasive ventilation failure, duration of MV, or ICU length of stay were observed. Hyperglycemia significantly increased in the steroid group (*Eur Respir J* 2014;43:717-24).
    d. A cohort study compared high-dose (greater than 240 mg/day) with low-dose (240 mg/day or less) methylprednisolone in more than 17,000 patients with an ECOPD admitted to an ICU. Patients in the high-dose group had longer ICU and hospital lengths of stay, higher hospital costs, longer durations of MV, and more hyperglycemia and fungal infections. Mortality did not differ between groups (Am J Respir Crit Care Med 2014;189:1052-64).
    e. An open-label, randomized, parallel-group trial compared fixed-dosed corticosteroid treatment (prednisone 40 mg/day) with variable-dosed corticosteroid treatment for 5 days for the treatment of ECOPD in 246 hospitalized patients. Those in the variable-dosed corticosteroid group received 61.4 mg/day of prednisone on average. In-hospital treatment failure was defined as death, need for MV, administration of additional rescue steroids or aminophylline, or upgrade of antibiotic use. Those in the variable-dosed group experienced a reduced risk of in-hospital treatment failure (RR 0.37 [0.18–0.74]). Post hoc analysis did not show a significant difference in treatment failure for patients receiving less than or greater than 60 mg/day (31.3% vs. 23.4% [p=0.351]); however, treatment failure was higher in patients receiving 40 mg or less per day, 44.4%, than for those receiving greater than 40 mg/day, 22.9% (p=0.27). This study suggests a more appropriate fixed steroid dose for ECOPD is prednisone 60 mg/day rather than 40 mg/day (Chest 2021;160:1660-9).

I. Antimicrobials (GOLD 2024; Cochrane Database Syst Rev 2018;10:CD010257)
1. Data are conflicting on which populations benefit from antimicrobials.
    a. A 2018 systematic review comparing antibiotics with placebo for ECOPD found a treatment failure relative risk of 0.72 (n=1191) among studies in outpatient settings using only antibiotics currently in practice. No differences in all-cause mortality or treatment failure were identified (Cochrane Database Syst Rev 2018;10:CD010257).
        i. Only one trial included ICU patients (Lancet 2001;358:2020-5).
            (a) Administration of antibiotics reduced treatment failure, all-cause mortality, and hospital length of stay.
            (b) Study limitations: Conducted in 2001; generalizability to current practice may be limited; study used ofloxacin, which is no longer used

        - ii. Data remain inconclusive regarding treatment failure, mortality, and repeated exacerbations for patients who are hospitalized outside the ICU with severe COPD and for outpatients.
        - iii. The findings within this systematic review are further limited by the inconsistency among studies in the description of COPD severity at baseline.
2. GOLD guidelines recommend 5–7 days of antibiotics during ECOPD in the following patient populations:
    - a. Patients with all three cardinal symptoms: increase in dyspnea, increased sputum, and sputum purulence
    - b. Patients with two cardinal symptoms if purulent sputum is one of the two symptoms
    - c. Patients requiring invasive or noninvasive MV for their respiratory insufficiency or failure as the result of an ECOPD
3. Choice of antimicrobial should be based on local resistance patterns.
    - a. Initial therapy with amoxicillin/clavulanate, macrolide, tetracycline, or quinolone is suggested by the guidelines. Considerations for antimicrobial selection should be guided by local resistance patterns.
    - b. For patients with frequent exacerbations, severe airflow obstruction, and/or exacerbations requiring MV, broader-spectrum antimicrobials should be considered because of the possible presence of *P. aeruginosa*.
4. De-escalation
    - a. Antimicrobial therapy should be de-escalated as appropriate according to culture results, if available.
    - b. Use of procalcitonin in critically ill patients with ECOPD is controversial. A study of ECOPD in ICU patients found that using a procalcitonin-based algorithm for initiating or discontinuing antibiotics was associated with a higher mortality rate compared with patients receiving standard antibiotic regimens (Intensive Care Med 2018;44:428-37).

J. Vitamin D
1. Mechanism of effect: Vitamin D metabolites attenuate inflammation and support immune system responses to pathogens.
2. The GOLD guidelines recommend routine identification and supplementation of vitamin D deficiency in patients hospitalized with ECOPD with vitamin D concentrations less than 10 ng/mL.
3. A systematic review and meta-analysis of three randomized controlled trials (469 patients with data available) showed that supplementation of vitamin D did not affect the rate of moderate/severe ECOPD (Thorax 2019;74:337-45).
    - a. Prespecified subgroup analysis of 87 patients identified that vitamin D supplementation reduced the rate of moderate to severe ECOPD in patients whose concentrations were deficient (25-hydroxyvitamin D concentrations less than 10 ng/mL) at baseline.
    - b. No effect on exacerbations for patients whose concentrations were not deficient at baseline
4. In a more recent randomized controlled trial of patients with COPD investigating the effects of vitamin D supplementation on exacerbations, a prespecified subgroup analysis of patients with vitamin D concentrations of 6–10 ng/mL compared with placebo found no difference in time to first exacerbation, time to hospitalization, or rate of exacerbations (Am J Clin Nutr 2022;116:491-9).

Patient Cases

7. A 79-year-old woman (weight 70 kg) is admitted to the ICU for the management of hypercapnic respiratory failure related to an ECOPD. She has had several admissions for ECOPD. The patient presents with fever, profound dyspnea, increased sputum production (thick and purulent), and confusion. She has a history of anaphylaxis to penicillin. Her blood pressure is 190/100 mm Hg, heart rate is 110 beats/minute, and respiratory rate is 22 breaths/minute. Her chest is hyperinflated and has poor air entry bilaterally. Her ABG values are as follows: pH 7.20, P_{CO_2} 85 mm Hg, and Pa_{O_2} 44 mm Hg on 6 L of nasal cannula. She is intubated and placed on MV. Which would be the most appropriate group of medications to treat this patient's severe ECOPD?
   A. Methylprednisolone 1 mg/kg intravenously administered as two divided doses, inhaled albuterol by nebulization, ampicillin/sulbactam 3 g intravenously every 6 hours for 7 days, and azithromycin 500 mg intravenously daily for 5 days.
   B. Prednisone 40 mg by nasogastric tube (NGT) daily for 5 days, inhaled albuterol and ipratropium by nebulization, ampicillin/sulbactam 3 g intravenously every 6 hours for 10 days, and azithromycin 500 mg daily intravenously for 5 days.
   C. Methylprednisolone 1 mg/kg intravenously administered as two divided doses, inhaled albuterol and ipratropium by nebulization, and levofloxacin 750 mg by NGT daily for 7 days.
   D. Prednisone 40 mg by NGT daily for 5 days, inhaled albuterol and ipratropium by nebulization, and levofloxacin 750 mg intravenously daily for 5 days.

8. A 75-year-old woman presents to the ED with a productive cough and altered mental status (oriented only to person). Her medical history is significant for type 2 diabetes and severe COPD. On physical examination, she has a productive cough and is alert and oriented × 4. Her vital signs are temperature 101.8°F, heart rate 95 beats/minute, respiratory rate 33 breaths/minute, systolic blood pressure 105 mm Hg, and Sp_{O_2} 86% on her home oxygen of 2 L/minute by nasal cannula. The patient is placed on noninvasive ventilation by Venturi mask at an F_{IO_2} of 40%, and her Sp_{O_2} is now 91%. A basic metabolic panel returns with SCr 1.3 mg/dL and serum urea nitrogen 55 mg/dL, and an ABG reports pH 7.37, Pa_{CO_2} 55 mm Hg, and Pa_{O_2} 59 mm Hg. Radiography reveals multilobar infiltrates. Which best describes the severity of the patient's ECOPD and her level of respiratory failure according to the 2024 GOLD guidelines?
   A. Moderate ECOPD with non–life-threatening acute respiratory failure.
   B. Moderate ECOPD with life-threatening acute respiratory failure.
   C. Severe ECOPD with life-threatening acute respiratory failure.
   D. Severe ECOPD with non–life-threatening acute respiratory failure.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: C**

The patient presents with a CF exacerbation, probably caused by an infection. The most likely causative organism of her infection is *P. aeruginosa*; therefore, therapy must be directed to *P. aeruginosa* (Answer B is incorrect). In addition, antibiotic treatment should include the empiric selection of two antibacterial agents, ideally a β-lactam and an aminoglycoside, dosed to effectively treat the infection (Answers A and D are incorrect). The ideal regimen should include a β-lactam dosed to treat *P. aeruginosa* – in this case, piperacillin/tazobactam at the recommended dose – and an aminoglycoside dosed once daily (Answer C is correct).

2. **Answer: B**

According to the STOP2 trial, patients who improve within 7 days of antimicrobial therapy can complete 10 days of antimicrobials. These patients' clinical outcomes are noninferior to those of patients who continue antimicrobials for 14 days (Answer B is correct). Answer A is incorrect; 7 days is too short for an exacerbation of CF. Answer C is incorrect, given the results of the STOP2 trial. Answer D is incorrect because microbiological cure is neither expected nor likely for patients with CF.

3. **Answer: D**

This patient has signs of right heart failure and rapid progression of symptoms, which place him in the high-risk category for mortality within 1 year (greater than 20%) (Answers A, B, and C are incorrect). In addition, he has symptoms at rest, which place him in WHO FC IV (Answer D is correct).

4. **Answer: A**

The patient's symptoms and physical findings place him in WHO FC IV. His unfavorable response to the vasodilator challenge makes CCBs an undesirable class of medications for him (Answer B is incorrect). Epoprostenol continuous infusion is indicated for patients with PAH presenting with WHO FC IV to improve symptoms, exercise capacity, and hemodynamics. In addition, it is the only treatment shown to reduce mortality in PAH (Answer A is correct). Macitentan and sildenafil could be considered in this patient; however, his elevated liver enzymes do not make macitentan an ideal agent (Answer C is incorrect). Intravenous sildenafil is also not ideal because of the hypotension associated with the intravenous formulation (Answer D is incorrect).

5. **Answer: C**

Risk factors for increased mortality in patients with asthma include (1) history of near-fatal asthma (e.g., requiring mechanical ventilation); (2) hospitalization or ED visit for asthma in the past year; (3) active use of oral corticosteroids or completion of recent course for asthma; (4) not currently using inhaled corticosteroids; (5) use of more than one canister of SABAs per month; (6) poor adherence to inhaled corticosteroid containing asthma medications and/or poor adherence to asthma action plan; (7) social history that includes major psychosocial problems or psychiatric illness; (8) food allergies; (9) comorbidities including pneumonia, diabetes, and arrhythmias. Two of the patient's listed characteristics are risk factors (Answer C is correct). Other answers include one risk factor or none (Answers A, B, and D are incorrect).

6. **Answer: C**

For life-threatening asthma exacerbations, SABAs, short-acting antimuscarinics, and intravenous corticosteroids are recommended (Answers A and B are incorrect). The recommended dose of intravenous corticosteroids is methylprednisolone 40 mg (equivalent to prednisone 50 mg) intravenously per day administered early in the course of the exacerbation (Answer C is correct; Answer D is incorrect).

7. **Answer: D**

The latest GOLD guidelines recommend systemic corticosteroids to shorten recovery time, improve FEV_1, and improve hypoxemia. The recommended dose is prednisone 40 mg orally once daily (or equivalent) for 5 days. Although recent data identified that some patients may have worse outcomes with fixed prednisone 40-mg doses, the data suggest prednisone 60 mg is adequate to balance the benefit of steroids with the risks of adverse effects (Answers A and C are incorrect). Adding inhaled SABAs (nebulized or MDI) with or without a short-acting anticholinergic is the preferred treatment in an ECOPD. Antibiotic treatment for 5–7 days is also indicated because the patient has signs of bacterial infection (fever, purulent sputum) and a severe ECOPD with respiratory failure. This patient has a history of anaphylactic reaction to penicillin and repeated exacerbations that may predispose her to resistant organisms such as *P. aeruginosa* (Answers A and B are incorrect); therefore, levofloxacin would be the best recommendation (Answer D is correct).

8. **Answer: A**

The current GOLD guidelines provide specific diagnostic parameters to determine the severity of an ECOPD. A respiratory rate greater than 24 breaths/minute and an Spo_2 less than 92% on home oxygen therapy clearly identify this patient as having either a moderate or severe asthma exacerbation. Patients with a moderate ECOPD may have hypercapnia ($Paco_2$ greater than 45 mm Hg) or hypoxia (Pao_2 less than 60 mm Hg); however, they have not yet developed acidosis (pH less than 7.35), whereas those experiencing a severe ECOPD have developed acidosis (Answers C and D are incorrect). Although the degree of respiratory failure is determined using many of the same parameters as the severity of ECOPD, there is a greater focus on patient response to therapy. An improvement in hypoxemia with noninvasive ventilation by Venturi mask with an Fio_2 greater than 35% and the absence of an altered mental status are associated with non–life-threatening respiratory failure (Answer B is incorrect; Answer A is correct).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: D**

It is imperative to recognize that this patient has acute respiratory distress syndrome (ARDS) caused by a CF exacerbation. Therefore, an inclusive therapy plan should include appropriate treatments for ARDS and CF. For ARDS, a lung-protective ventilation strategy (tidal volume 4–6 mL/kg) and a fluid-conservative strategy (CVP less than 4 mm Hg, if not in shock) are of utmost importance (Answers A and C are incorrect because of the CVP goal; Answer D is correct). Appropriate treatment of the CF exacerbation includes empiric therapy for *P. aeruginosa* in the form of optimal doses of a β-lactam and aminoglycoside (Answer B is incorrect because of the inappropriate tobramycin dose and CVP goal of 10–14 mm Hg).

2. **Answer: D**

The highest quality of evidence for improved outcomes with CF exacerbations is with adjunctive therapy for mucous clearance. The guidelines recommend airway clearance options such as aggressive chest physical therapy, nebulized dornase alfa, and hypertonic saline as a grade B recommendation (Answer D is correct). Hypertonic saline would be appropriate, but nebulization of normal saline is not included in any of the recommendations (Answer A is incorrect). Both corticosteroid administration and concurrent administration of intravenous and inhaled antibiotics have a grade I recommendation, meaning evidence is insufficient to support them (Answers B and C are incorrect).

3. **Answer: D**

This patient presents with severe right heart failure. The primary goal is to optimize RV preload by maintaining a net negative fluid balance using gentle diuresis and blood pressure monitoring (Answer D is correct). Dopamine would increase blood pressure; however, it might worsen the patient's tachycardia, thereby worsening her already tenuous clinical status (Answer A is incorrect). Epoprostenol would help decrease pulmonary pressures; however, epoprostenol would potentially worsen the patient's blood pressure because of its peripheral vasodilating effects (Answer B is incorrect). Phenylephrine would not be optimal because this vasopressor might worsen RV function, further elevate pulmonary artery pressure by α1-receptors in the pulmonary vasculature, and potentially induce a reflex bradycardia (Answer C is incorrect).

4. **Answer: C**

Treatment goals for PAH include, but are not limited to, achieving and maintaining WHO FC I or II (Answer A is incorrect), preserving 6MWD to greater than 440 m (Answer B is incorrect), and preserving RV size and function (right atrial pressure less than 8 mm Hg and cardiac index 2.5 L/minute/m^2 or greater) (Answer C is correct). The clinician should normalize BNP to less than 50 ng/L (Answer D is incorrect).

5. **Answer: C**

This patient has shortness of breath at rest that is interfering with his conversational ability, and his FEV_1 is less than 50% of predicted; therefore, his asthma exacerbation would be classified as severe (Answer C is correct). FEV_1 would be greater than 50% in mild/moderate asthma exacerbation (Answers A and B are incorrect). In a life-threatening asthma exacerbation, the patient would have symptoms such as drowsiness, confusion, or silent chest. This patient could progress to life threatening but currently would not be classified as such (Answer D is incorrect).

6. **Answer: B**

This patient presents with near-fatal asthma that is unresponsive to initial therapy. Magnesium sulfate (2 g intravenously administered over 20–30 minutes) can be considered in patients who have life-threatening exacerbations and are unresponsive to conventional therapies after 1 hour (Answer B is correct). Antimicrobials are not routinely recommended for asthma exacerbations if the patient has no evidence of concurrent infection (Answer A is incorrect). Because of the lack of improved outcomes, risk of adverse effects, and superior bronchodilation with SABAs, methylxanthines (theophylline and aminophylline) are not recommended for acute asthma exacerbations (Answer C is incorrect). Mucolytic agents are irritating and may worsen cough and airflow obstruction (Answer D is incorrect).

7. **Answer: B**

The recommended corticosteroid dose for an ECOPD is prednisone 40 mg orally once daily (Answer D is incorrect; Answer B is correct). Antimicrobial treatment should be initiated if (1) all three cardinal symptoms of an ECOPD (increased dyspnea, increased sputum production, and increased sputum purulence) are present; (2) two of the three cardinal signs are present, with increased sputum purulence as one of the symptoms; or (3) the patient requires noninvasive or invasive ventilation. This patient has no indication for antimicrobials (Answers A and C are incorrect).

8. **Answer: D**

Although the GOLD-recommended dose of steroids for an ECOPD is prednisone 40 mg orally (or intravenously), some studies that included populations of ICU patients have shown higher doses may be needed or may be tolerated with some increase in adverse effects. Currently, doses higher than prednisone 40 mg have not been linked to increased mortality (Answer A is incorrect). A recent investigation identified significant racial bias in the use of peripheral Sa_{O_2} because of frequent overestimation of Sa_{O_2} compared with a direct ABG measurement for patients with darker skin tones. This answer is incorrect because the publication did not investigate patient outcomes. This patient has a higher Sp_{O_2} measure than the patients in the study (92%–96%), who had a high rate of hypoxemia identified on ABG. Answer C is incorrect because no specific dose of macrolide has been linked to mortality, and azithromycin 500 mg intravenously once is the recommended loading dose. Answer D is correct because titrating oxygen therapy to peripheral Sa_{O_2} greater than 88%–92% has been linked to mortality. The correct intervention would have been to decrease the Fi_{O_2} when the patient had an Sa_{O_2} greater than 92%.

Toxicology

Kyle Weant, Pharm.D., FCCP, BCPS, BCCCP, BCEMP

University of South Carolina College of Pharmacy
Columbia, South Carolina

TOXICOLOGY

KYLE WEANT, PHARM.D., FCCP, BCPS, BCCCP, BCEMP

UNIVERSITY OF SOUTH CAROLINA COLLEGE OF PHARMACY
COLUMBIA, SOUTH CAROLINA

Learning Objectives

1. Distinguish between the common clinical toxidromes associated with acute poisonings.
2. Describe the general management of a patient with an acute overdose.
3. Determine the best options for the management of selected toxins.
4. Develop a patient care plan for a patient presenting with an acute overdose.
5. Identify the adverse effects and monitoring of the patient who is poisoned.

Abbreviations in This Chapter

ABC	Airway, breathing, and circulation
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CB1	Cannabinoid-1
CB2	Cannabinoid-2
CIWA	Clinical Institute Withdrawal Assessment for Alcohol Scale
CK	Creatine kinase
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
ED	Emergency department
GABAa	γ-aminobutyric acid
GI	Gastrointestinal
HIET	Hyperinsulinemic euglycemic therapy
HR	Heart rate
ICU	Intensive care unit
INR	International normalized ratio
NAPQI	*N*-acetyl-*p*-benzoquinoneimine
NMDA	N-methyl-D-aspartate
RR	Respiratory rate
SBP	Systolic blood pressure
SCr	Serum creatinine
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 38-year-old woman with type 2 diabetes is admitted for confusion and altered mental status. She has an active prescription for glipizide 10 mg by mouth twice daily, but she cannot respond to further questioning. Her vital signs are as follows: blood pressure (BP) 115/65 mm Hg, heart rate (HR) 68 beats/minute, respiratory rate (RR) 15 breaths/minute, and temperature 98.6°F (37°C). Her point-of-care glucose concentration is 45 mg/dL, and she is given 50 mL of 50% dextrose in water intravenously twice. Her follow-up point-of-care glucose concentration is 50 mg/dL after the first dose and 57 mg/dL after the second dose, with no improvement in symptoms. Which is the most appropriate intervention at this time?
   A. Dextrose.
   B. Glucagon.
   C. Octreotide.
   D. Sodium bicarbonate.

2. A 56-year-old man is admitted to the intensive care unit (ICU) after a β-blocker overdose. After administering 2 L of 0.9% sodium chloride and 3 g of calcium gluconate, his vital signs are as follows: BP 70/40 mm Hg, HR 52 beats/minute, and RR 22 breaths/minute. Which therapy is most appropriate at this time?
   A. Glucagon 5 mg intravenously.
   B. Atropine 2 mg intravenously.
   C. Insulin 0.1 unit/kg intravenously.
   D. Dopamine 2 mcg/kg/minute intravenously.

3. A 76-year-old woman is admitted to the emergency department (ED) with the chief concern of decreased mental status. Her vital signs are as follows: BP 118/72 mm Hg, HR 57 beats/minute, and RR 17 breaths/minute. She is experiencing nausea, but her physical examination is otherwise normal. Her husband is concerned that she may not be taking her medications properly. Given her presentation, which common toxidrome is the patient most likely experiencing?

A. Anticholinergic.
B. Cholinergic.
C. Opioid.
D. Sympathomimetic.

4. A 38-year-old woman is admitted to the ICU after a suspected overdose of risperidone. She was initially hypotensive, but she was stabilized after the administration of two 500-mL boluses of lactated Ringer solution. Her BP is now 118/77 mm Hg, HR 75 beats/minute, and RR 16 breaths/minute. A 12-lead electrocardiogram (ECG) shows QT prolongation (corrected QT interval [QTc] = 480 milliseconds), and her chemistry panel is significant for a bicarbonate of 24 mEq/L, potassium of 3.1 mEq/L, and magnesium of 1.8 mg/dL. Which intervention is most appropriate at this time?

   A. Potassium chloride 20 mEq every hour for two doses.
   B. Activated charcoal 50 g.
   C. Magnesium sulfate 2 g.
   D. Lorazepam 2 mg.

5. A 48-year-old man is admitted to the medical floor for community-acquired pneumonia. His medical history is significant for hypertension, hyperlipidemia, and chronic obstructive pulmonary disease (COPD), and he reports occasional alcohol use but no history of alcohol withdrawal. He is initiated on levofloxacin 750 mg intravenously daily and nebulizer treatments with albuterol and ipratropium. Twenty-four hours after admission, he is increasingly more confused and has nausea and vomiting. His vital signs are stable: BP 115/68 mm Hg, HR 122 beats/minute, RR 21 breaths/minute, and temperature 99.7°F (37.6°C). The team is concerned about possible alcohol withdrawal and asks for recommendations for initial therapy. Which is the most appropriate treatment for this patient?

   A. Lorazepam 2 mg intravenous push every 4 hours as needed according to the patient's Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA) score.
   B. Phenobarbital 65 mg by mouth every 8 hours as needed according to the patient's CIWA score.
   C. Propofol continuous infusion.
   D. Clonidine 0.1 mg by mouth every 12 hours.

6. A 57-year-old male patient on the medical floor is incorrectly administered a dose of methadone 40 mg by mouth that was written for the patient in the adjoining bed. Two hours later, the nurse finds him unresponsive with the following vital signs: BP 105/67 mm Hg, HR 61 beats/minute, RR 8 breaths/minute, and temperature 98.7°F (37.1°C). The nurse calls for the rapid response team, and, as the team pharmacist, you are asked for a recommendation. Which treatment is most appropriate at this time?

   A. Activated charcoal 50 g orally.
   B. Naloxone 0.04 mg intravenously.
   C. Whole bowel irrigation orally.
   D. 1 L of 0.9% sodium chloride intravenously.

Questions 7 and 8 pertain to the following case.
A 56-year-old female patient is admitted to the ED after an intentional overdose of 25 amlodipine 10-mg tablets. She is given activated charcoal 50 g, 2 L of 0.9% sodium chloride, and 3 g of calcium gluconate. Her current vital signs are as follows: BP 90/50 mm Hg, HR 107 beats/minute, RR 17 breaths/minute, and temperature 98.7°F (37.1°C). Serum chemistries are as follows: Na 141 mEq/L, K 2.5 mEq/L, Cl 101 mEq/L, HCO_3 24 mEq/L, blood urea nitrogen (BUN) 19 mg/dL, serum creatinine (SCr) 0.9 mg/dL, and glucose 215 mg/dL. The ED physician wants to initiate hyperinsulinemic euglycemic therapy (HIET).

7. Which is most appropriate to initiate or do first with respect to HIET?

   A. Give insulin 1 unit/kg intravenously.
   B. Give 50 mL of 50% dextrose in water intravenously.
   C. Warn the physician that full effects may take up to 30 minutes.
   D. Give 20 mEq of potassium chloride intravenously every hour for four doses.

8. The patient is not responding to HIET initiation. Her current infusion rate is 1 unit/kg/hour. Her BP remains low at 70/40 mm Hg, and her HR is now 58 beats/minute. Her repeat glucose is 186 mg/dL. Which is most appropriate to initiate at this time?

   A. Discontinue HIET, and initiate norepinephrine.
   B. Continue HIET, and increase the insulin infusion rate and initiate norepinephrine.
   C. Continue HIET, and initiate epinephrine.
   D. Discontinue HIET, and begin intravenous lipid therapy.

BPS Critical Care Pharmacy Examination Content Outline

This chapter covers the following sections of the Critical Care Pharmacy Examination Content Outline:

1. Domain 1: Critical Care
    a. Task A: 1, 2, 3, 6
    b. Task B: 3, 4
2. Domain 2: Therapeutics and Managment
    a. Task B: 2, 3, 4, 9, 11, 15
    b. Task C: 1, 2, 3, 4
3. Domain 3: Professional Practice
    a. Task A: 1
    b. Task B: 1, 4

I. EPIDEMIOLOGY

A. Population based: The American Association of Poison Control Centers releases an annual report based on all the cases submitted by the 55 regional poison centers to the National Poison Data System to help clinicians stay abreast of the changing landscape of exposures (Clin Toxicol 2023;61:717-939). The data contained within this chapter were published in 2023 and contain cases from 2022. The most recent annual reports can be found at https://www.poisoncenters.org/annual-reports.

1. In 2022, 2,064,875 human exposures were reported. Fatalities were reported in 1491 cases (Table 1).
2. The most common site of exposure was a residence (90.7%), followed by workplace (1.93%) and other's residence (1.81%).
3. Most of the reported cases (1,159,170) occurred in children, defined in the report as younger than 20 years. To add perspective, 968,189 cases were reported in children 12 years and younger.
4. The most common reasons associated with these exposures were unintentional (76.4%), intentional (18.9%), and adverse reactions (2.7%). Of note, therapeutic errors accounted for 331,539 (16.1%) of all cases. The scenarios reported for therapeutic errors included inadvertent double dosing (30.8%), incorrect dose (16.4%), incorrect medication administered or taken (15%), doses administered too close in time (11.1%), and inadvertent exposure to another person's medication (8.5%).
5. Routes of exposure included ingestion (82.7%), inhalation/nasal (7.6%), dermal (6.9%), and ocular (4.1%). Of the 1491 exposure-related fatalities, most were by ingestion (83.4%), followed by inhalation/nasal (7.3%) and parenteral (2.7%).

B. Management based

1. Only 30.6% of exposures were managed in a health care facility, with 3.4% managed in critical care units.
2. Gastric decontamination was used in about half of all exposures (49.9%); however, antidotes were given in only 12.4% of the exposures. The most common gastric decontamination strategy was the use of activated charcoal (1.6% of total exposures), followed by other emetic agents (0.9%), cathartics (0.1%), whole bowel irrigation (0.05%), and gastric lavage (0.02%).

Table 1. Top 5 Most Common Medication-Related Toxic Exposures in 2022

Most Common Medication-Related Toxic Exposures	% of Total Cases
All human exposures	
Analgesics	11.51
Antidepressants	5.61
Antihistamines	4.81
Cardiovascular drugs	4.74
Sedatives/hypnotics/antipsychotics	4.60
Adult exposures (≥ 20 yr of age)	
Analgesics	11.09
Sedatives/hypnotics/antipsychotics	7.37
Antidepressants	7.30
Cardiovascular drugs	7.06
Alcohols	4.39
Anticonvulsants	3.81
Pediatric exposures (< 6 yr of age)	
Analgesics	9.54
Dietary/herbal/homeopathic supplements	6.65
Antihistamines	5.03
Vitamins	4.85
Topical preparations	4.06

Information from: Gummin DD, Mowry JB, Beuhler MC, et al. 2022 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 40th annual report. Clin Toxicol 2023;61:717-939.

II. EMERGENCY EVALUATION AND MANAGEMENT

A. The primary treatment strategy for managing a toxic exposure should focus on stabilizing the patient, with an emphasis on airway, breathing, and circulation (ABC). The most common factor contributing to death from a poisoning or drug overdose is the loss of the protective reflexes of the airway secondary to flaccid tongue, aspiration of gastric contents into the lungs, or respiratory compromise including arrest. Emergent endotracheal intubation should be performed when necessary. Vital signs (HR, RR, BP, temperature, and oxygen saturation) and changes in mental status should be closely monitored. After stabilization, the DEFG approach can be considered:
D: Decontamination
E: Enhanced elimination
F: Focused antidote therapy
G: Get help from a poison control center or toxicologist

B. Supportive care should be based on specific patient symptoms and may include the administration of intravenous fluids, supplemental oxygen, and advanced airway management. Other potential complications should be assessed, such as presence of rhabdomyolysis, rigidity, or dystonia. Additional tests, such as a 12-lead ECG, chest radiograph, or electroencephalogram may be required. In addition, essential laboratory tests should be conducted and assessed for the presence of an osmolar gap, anion gap acidosis, hyper/hypoglycemia, hyper/hyponatremia, hyper/hypokalemia, renal failure, and liver failure.
   1. Use of "coma cocktail" preparations is controversial and therefore not routinely recommended because they should not replace or substitute for a thorough analysis of the patient (JEMS 2002;27:54-60). Formulations vary, but they typically contain one or more of the following: dextrose, thiamine, and naloxone. The following text presents an overview of the common additives, a rationale for use, and potential controversies.
      a. Dextrose 50%, 12.5–25 g (25–50 mL) intravenously is administered to treat hypoglycemia; it is recommended to perform point-of-care blood glucose testing to confirm before administration.
      b. Thiamine 100 mg is administered intravenously to prevent Wernicke encephalopathy; often under-recognized, several doses of high-dose parenteral thiamine (e.g., 500 mg) concurrent with or immediately following intravenous dextrose before intravenous dextrose are typically required to effectively treat (J Emerg Med 2012;42:488-94).
      c. Naloxone 0.04–2 mg IV is administered in a stepwise titration to reverse respiratory depression secondary to opiate overdose.

C. Ingestions
   1. A thorough physical examination should be performed.
   2. A medication history and reconciliation should be done, including all prescription medications, over-the-counter agents, illicit substance use, and herbal products.
   3. The history of the ingestion should be determined, if possible, including the following elements (Ann Emerg Med 1999;33:735-56):
      a. Timing and route of the exposure, the possible agents involved and their strengths and amounts, and the potential intent of the patient
      b. History from the prehospital care providers, family members, or other patient advocates
      c. Onset and progression of any symptoms
   4. Some providers advocate for the use of toxidromes, which are a collection of symptoms that occur with particular classes of toxic agents. Toxidromes may help identify the toxic agent and assist in care by helping providers anticipate additional symptoms. Although they may be very useful in the care of an acute poisoning, they should be used with caution because some symptoms may overlap with other classes of toxins, may be impacted by comorbid conditions, or may be absent altogether.

5. Common Toxidromes and Presentation (Chest 2011;140:795-806) (Crit Care Clin 2012;28:180-198)
    a. Anticholinergic
        i. Mechanism of toxicity is through competitive antagonism of the effects of acetylcholine at peripheral muscarinic receptors and central receptors.
        ii. Signs and symptoms include altered mental status, delirium, hallucinations, mumbled speech, dry mucous membranes, mydriasis, anhidrosis, flushing, hyperthermia, tachycardia, hypoactive bowel sounds, and urinary retention.
        iii. Common drugs that have anticholinergic activity include antihistamines, antipsychotics, tricyclic antidepressants, and skeletal muscle relaxants.
    b. Cholinergic
        i. Mechanism of toxicity is inhibition of acetylcholinesterase causing accumulation of acetylcholine ultimately resulting in overstimulation of muscarinic and nicotinic receptors.
        ii. Signs and symptoms include confusion, central nervous system (CNS) depression, miosis, wet mucous membranes, salivation, lacrimation, diaphoresis, emesis, urination, diarrhea, muscle weakness/twitching, bronchospasm, bronchorrhea, hypertension, tachycardia, and bradycardia.
        iii. Common drugs that have cholinergic activity include organophosphates, nerve agents, nicotine, pilocarpine, and physostigmine.
    c. Opioid
        i. Mechanism of toxicity is stimulation of opioid receptors causing a decrease in autonomic activity.
        ii. Signs and symptoms include sedation, miosis, decreased bowel sounds (ileus), respiratory depression, hypotension, and bradycardia.
        iii. Common drugs that have opioid activity include heroin, morphine, codeine, synthetic opioids, loperamide, and dextromethorphan (in large quantities).
    d. Sympathomimetic
        i. Mechanism of toxicity is through an increase in sympathetic tone through release of cathecholamines, inhibition of reuptake, by direct receptor stimulation, and alterations in neurotransmitter metabolism.
        ii. Signs and symptoms include agitation, delirium, mydriasis, diaphoresis, myoclonus, hyperthermia, hypertension, and tachycardia.
        iii. Common drugs that have sympathomimetic activity include cocaine, methamphetamine, pseudoephedrine, and caffeine.
6. Drug screens are used in acute toxic ingestions, the most common of which is the qualitative urine screen. This method tests for the presence of a substance, but it cannot detect the amount of substance present. If a toxin is known, a quantitative drug screen may be used to confirm the exact amount present. Although urine drug screens may vary by institution, they may include amphetamines, barbiturates, benzodiazepines, cocaine, MDMA (ecstasy), methamphetamines, opiates, THC (marijuana), and tricyclic antidepressants (TCAs). Urine screens are not considered comprehensive; therefore, the presence of additional agents should be tested for (e.g., acetaminophen, salicylates). However, comprehensive drug screens using gas chromatography and liquid chromatography together with mass spectrometry can be used in patients presenting with severe or unexplained toxicity.
    a. A negative screen does not exclude the presence of a toxic substance, especially if the presumed agent is not present on the screen. Many agents are not identified by their designated screen; this is especially an issue with standard amphetamine, benzodiazepine, and opiate screens.

b. A positive test also does not necessarily confirm the diagnosis because another agent may be present but at concentrations below a detectable threshold. In addition, a positive test does not indicate that the patient is intoxicated on the particular substance (e.g., cocaine is positive for 3 days; however, its effects last only a few hours) or that the agent ingested is the exact agent that is screened (e.g., bupropion causes a false-positive amphetamine screen) (Am J Health Syst Pharm 2010;67:1344-50).

Patient Case

1. A 53-year-old man (height 74 inches, weight 97 kg [215 lb]) arrives in the ED confused and disoriented. He cannot provide any information about his condition or medical history. Vital signs are as follows: BP 85/50 mm Hg, HR 120 beats/minute, RR 28 breaths/minute, and temperature 99.2°F (37.3°C). On physical examination, an unmarked pill bottle is found in his pocket. Two tablets remain, and a possible drug overdose is suspected. Which is most appropriate to do first for this patient?
   A. Send a quantitative urine drug screen.
   B. Stabilize the patient's ABC.
   C. Order a coma cocktail.
   D. Try to identify the tablets in a drug database.

III. GASTRIC DECONTAMINATION/ENHANCED ELIMINATION

A. Many strategies for gastric decontamination are used to try to remove toxins or prevent further absorption. No particular strategy is preferred to another; each has certain advantages and disadvantages, and the risks and benefits must be considered before use. Consensus statements from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists recommend against the routine use of any decontamination strategy but suggest that these strategies play a role in individualized care after a poison exposure (Clin Toxicol 2013;51:127). Table 2 lists the common dosing strategies for general decontamination and enhanced elimination.

B. Ipecac
   1. Ipecac is no longer manufactured in the United States since 2010 and is no longer recommended because of concerns for safety and ability to improve outcomes for patients who have been poisoned.
   2. Mechanism of action is to induce vomiting through irritation of the gastric mucosa and stimulation of the chemoreceptor trigger zone in the medulla.
   3. Guidelines recommend ipecac (if available) to be given only under a specific recommendation from a poison control center, ED physician, or other qualified medical personnel when all the following conditions are met (Clin Toxicol 2013;51:134-9; Clin Toxicol 2005;43:1-10):
      a. No specific contraindication exists for use.
      b. There is a substantial risk of serious toxicity of the toxin to the patient.
      c. No alternatives are available or considered effective to reduce the toxin absorption.
      d. A delay of more than 1 hour is expected before arrival to a medical facility.
      e. Use of ipecac will not adversely affect a more definitive treatment option.

C. Gastric Lavage
  1. Gastric lavage is performed by inserting a larger-bore orogastric or nasogastric catheter tube (36–40 French for adults and 24–28 French for children) with several holes at the distal end into the stomach. Aliquots of warmed tap water (200–300 mL) are then instilled until there is clearing of aspirated fluid.
  2. The efficacy is highly variable and diminishes over time; therefore, it is optimal to perform within 60 minutes of ingestion.
  3. Guidelines emphasize that gastric lavage has not been proven to decrease the severity of illness, improve recovery times, or improve outcomes (Clin Toxicol 2013;51:140-6).
  4. Should be considered only for life-threatening ingestions when it can be safely performed within 30–60 minutes of ingestion.
  5. Even in life-threatening overdoses, it may not be beneficial. Gastric lavage should not be performed routinely, if at all, for treating the patient who is poisoned. In the rare situation when it might be appropriate, clinicians should consider treatment with activated charcoal or observation and supportive care in place of gastric lavage (Clin Toxicol 2013;51:140-6).
  6. Contraindications for gastric lavage include patients with craniofacial abnormalities, concomitant head trauma, unprotected airway, increased risk of aspiration, those at risk of GI hemorrhage or perforation and caustic ingestion such as acids (e.g., boric acid) and alkalis (e.g., dishwasher detergents) because of the risk of exacerbating any esophageal or gastric injury. Patients with decreased consciousness require endotracheal or nasal intubation before the procedure.
  7. Complications associated with gastric lavage include aspiration, laryngospasm, perforation of the esophagus or stomach, arrhythmias, fluid imbalance, hyponatremia, and small conjunctival hemorrhages.

D. Cathartics
  1. Used to reduce the transit time of toxins and hence absorption, as well as in combination with activated charcoal to decrease constipating effects
  2. Cathartics have conflicting data regarding decreased transit time in the GI tract and have no data to support improved patient outcomes (J Toxicol Clin Toxicol 2004;42:243-53).
  3. Cathartic use is not recommended; if used, it should be limited to a single dose and not be used as monotherapy.
  4. Contraindications to cathartic use include absence of bowel sounds, recent GI surgery, intestinal perforation or obstruction, hypotension, electrolyte disturbances, and renal insufficiency (for magnesium-based cathartics).
  5. Complications include nausea, dehydration, hypotension, and magnesium imbalances.

E. Activated Charcoal
  1. Activated charcoal is an adsorbent that works by binding the toxin throughout the GI tract to reduce systemic absorption. Although activated charcoal binds most substances, Table 3 lists the agents for which activated charcoal is NOT recommended.
     a. This therapy should be avoided with acids and alkalis because charcoal may cause vomiting, which can be damaging in these ingestions. The black color and thickness of the activated charcoal may also cause discoloration of the stomach lining and therefore interfere with endoscopy.
     b. Alcohols bind poorly; therefore, large doses are needed, which are difficult to ingest.
     c. Cyanide will bind, but not with as much activity as other substances. Because the toxic dose of cyanide is so small, normal doses of activated charcoal may be ineffective.
     d. Hydrocarbons may lead to a significant risk of aspiration.

2. It is optimal to administer activated charcoal within 60 minutes of the toxin ingestion to maximize efficacy.
3. The use of a cathartic (e.g., sorbitol) in combination with activated charcoal is not recommended.
4. If significant nausea occurs, it is recommended to administer an antiemetic. When choosing an antiemetic, potential drug and symptom interactions should be considered as well.
5. Complications include aspiration, accidental administration into the lung, emesis, constipation, and gastric obstruction.
6. Contraindications include an unconscious state or an inability to otherwise protect the airway without endotracheal intubation, ileus or intestinal obstruction, late presentation (more than 2 hours), and recent GI surgery.
7. Multidose activated charcoal is a method described to enhance the elimination of certain toxins. It is not more effective in reducing morbidity or mortality than single-dose charcoal, but it may be administered to enhance elimination in life-threatening ingestions caused by medications that undergo significant enterohepatic recirculation with active enterohepatic metabolites (J Toxicol Clin Toxicol 1999;37:731-51).

F. Whole Bowel Irrigation
   1. Whole bowel irrigation is a strategy for cleansing the bowel to remove potential toxins by administering an osmotic polyethylene glycol solution.
   2. Not recommended for routine use, but may be useful in potentially life-threatening ingestions of medications with long half-lives, sustained-release dosage forms, or enteric-coated formulations. Specifically useful for certain toxic substances not adsorbed by activated charcoal (e.g., lithium and iron). May also be beneficial for iron overdoses and for “packers” of illicit substances.
   3. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the efficacy of charcoal.
   4. Complications of the polyethylene glycol electrolyte solutions include anaphylaxis, angioedema of the lips, aspiration, Mallory-Weiss tear, and esophageal perforation.
   5. Contraindications include bowel obstruction, perforation, ileus, and use in patients with recent bowel surgery. A kidney-ureter-bladder radiograph may be used to rule out these contraindications.

G. Urine Alkalinization
   1. Urine alkalinization is a strategy to improve the elimination of toxins by increasing the urine pH to levels of 7.5 or greater via administration of sodium bicarbonate or sodium acetate (J Toxicol Clin Toxicol 2004;42:1-26).
   2. Specific substances that may benefit from this strategy include salicylates, phenobarbital, chlorpropamide, and other weak acids with intrinsic urinary clearance.
   3. Contraindications include acute and chronic renal failure and preexisting heart failure owing to the volume of fluid required for this treatment strategy.
   4. Complications include hypokalemia, hypernatremia, hypocalcemia, cerebral vasoconstriction, and coronary vasoconstriction.
   5. To deploy urine alkalinization therapy, it is recommended to check baseline blood chemistries, electrolyte values, and an arterial blood gas, as well as to correct any fluid or electrolyte deficits (especially potassium because alkalemia will push potassium intracellularly). Hypokalemia will make it impossible to get the urine alkaline because of the K+-H+ exchange in the kidneys, which will excrete H+ into urine if K+ is low.
   6. Guideline-recommended monitoring includes urine pH every 15–30 minutes (every 30–60 minutes is more accepted in clinical practice) until the goal pH level of 7.5–8.5 is achieved, followed by every hour; serum potassium concentrations, central venous pressure, and arterial blood gases should be measured hourly.

Table 2. Common Dosage Strategies for General Decontamination and Enhanced Elimination

Decontamination/ Elimination Strategy	Pediatric Dosing	Adult Dosing
Gastric lavage[a]	10-mL/kg aliquots, followed by return of an equal amount	200- to 300-mL aliquots, followed by return of an equal amount
Cathartics		
Magnesium citrate:	4 mL/kg	240 mL
Sorbitol:	4.3 mL/kg (35% solution)	1–2 mL/kg (70% solution)
Activated charcoal		
Single dose	Up to 1 yr of age: 0.5–1 g/kg (usually 10–25 g) 1–12 years: 0.5–1 g/kg (usually 25–50 g)	> 12 years and adults: 25–100 g (doses > 50 g may induce vomiting)[b]
Multidose	0.5–1 g/kg (25–50 g), followed by 0.25–0.5 g/kg (10–25 g) every 4 hr	50 g, followed by 25–50 g every 4 hr
Whole bowel irrigation[c]	9 mo to 6 yr: 500 mL/hr 6–12 yr: 1000 mL/hr	> 12 yr and adults: Goal is 2000 mL/hr (initiated at 500 mL/hr and doubled every 30 min)
Urine alkalinization with sodium bicarbonate[d]	25–50 mEq intravenously for 1 hr	250 mEq intravenously for 1 hr

[a] Sterile water or 0.9% sodium chloride; may repeat until the return fluid is clear and absent of particulate matter.

[b] Upper limit may vary depending on the capacity of the stomach.

[c] Polyethylene glycol electrolyte lavage solutions; dose until the rectal effluent is clear or the desired effect has been achieved.

[d] Sodium bicarbonate in dextrose 5% in water additional boluses can be given hourly (or begin a continuous infusion at this hourly rate) to maintain a urine pH of 7.5–8.5.

Table 3. Agents for Which Activated Charcoal Is NOT Recommended

Substance	Examples
Acids	Boric acid, mineral acids
Alcohols	Ethanol, ethylene glycol, methanol
Alkalis	Bleach, cleaning solutions, dishwasher detergents, lye
Carbamates	Insecticides, neostigmine, physostigmine
Cyanide	Cyanogen chloride, hydrogen cyanide, potassium cyanide, sodium cyanide
Hydrocarbons	Gasoline, kerosene, petroleum oils
Metals	Arsenic, iron, lead, lithium, mercury
Organic solvents	Acetic acid, acetone, ethylene glycol, glycerin, toluene
Organophosphates	Antihelminthic drugs (trichlorfon), insecticides (malathion, parathion), herbicides

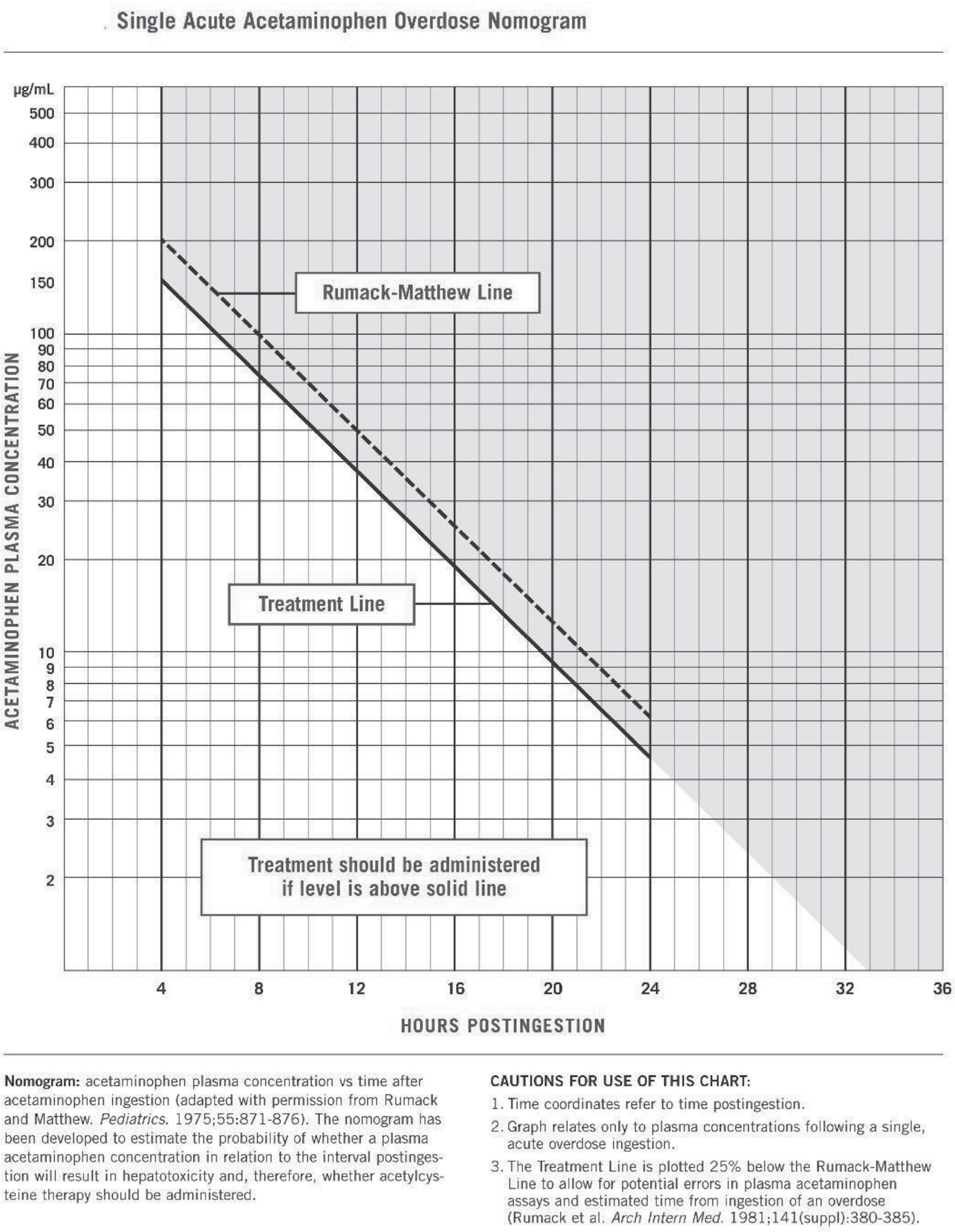
IV. ACETAMINOPHEN

A. Background
   1. Acetaminophen is consistently one of the most common toxic drug exposures.
   2. Accounted for 66,710 exposures (as a single agent) and resulted in 167 deaths in 2022.
   3. In general, acute doses of 150 mg/kg or 7.5 g in adults and 200 mg/kg in children are considered toxic. It is recommended that doses exceeding this threshold be managed in a health care facility.
   4. The mechanism of toxicity is caused by the active metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which can lead to oxidant cell injury, hepatic failure, and death.
   5. Around 90% of acetaminophen undergoes phase II conjugation to glucuronide and sulfate conjugates that are excreted in the urine. An additional 2% is excreted unchanged in the urine. The remaining amount (8%–10%) is converted by cytochrome P450 (CYP2E1) to NAPQI. NAPQI is normally converted by glutathione to cysteine conjugates, which are renally excreted. In an overdose, the sulfation and glucuronidation pathways become saturated, leading to glutathione depletion and a subsequent buildup of NAPQI (Clin Liver Dis 2013;17:587-607).

B. Clinical Presentation – Four clinical phases are associated with acetaminophen toxicity (time intervals are estimated and may vary with individual patients).
   1. Phase I occurs within the first 24 hours after ingestion. Patients may present with minimal or no signs of distress. Potential signs and symptoms include nausea, vomiting, diaphoresis, and anorexia.
   2. Phase II occurs 24–48 hours after exposure and is marked by initial damage to the hepatocytes. Patients may present with right upper quadrant pain, increases in liver transaminases, elevated total bilirubin concentrations, and prolonged prothrombin time.
   3. Phase III occurs 72–96 hours after initial exposure and is the peak of the hepatotoxic effects. Patients may present with lactic acidosis, acute renal failure, acute pancreatitis, and fulminant hepatic failure, as evidenced by jaundice, extensive coagulopathies, hypoglycemia, and hepatic encephalopathy.
   4. Phase IV occurs about 1 week after exposure and marks the recovery phase if the patient survives phase III.

C. Treatment
   1. The goal of treatment is to prevent the development of hepatic toxicity and reduce mortality.
   2. Gastric decontamination with a single dose of activated charcoal can be considered if the patient presents within the first hour after exposure, is not vomiting, and has no alterations in mental status. However, with the availability of highly efficacious antidotal therapy, the risks often outweigh the benefits.
   3. Antidote therapy is recommended with acetylcysteine. The mechanism of action for acetylcysteine is to increase the synthesis and bioavailability of glutathione, substituting for glutathione by binding to the reduced sulfur group of NAPQI, and supplying a substrate for sulfation, thereby increasing nontoxic metabolism. Additional mechanisms of action have also been proposed, including its facilitation of reactive oxygen and nitrogen species scavenging.
   4. Guidelines suggest that acetylcysteine treatment be administered to patients within the first 8 hours of exposure if they can be stratified as being at possible or probable risk of hepatotoxicity by the Rumack-Matthew nomogram (Figure 1). If patients cannot be stratified because of unknown time of ingestion, they should receive acetylcysteine if any of the following conditions apply: significantly elevated alanine aminotransferase (ALT) concentration, serum acetaminophen concentrations greater than 20 mcg/mL, or history of chronic ingestions exceeding 4 g/day with an elevated serum ALT concentration and/or presenting more than 24 hours post-ingestion with evidence of hepatotoxicity (Ann Emerg Med 2007;50:292-313).
      a. This includes patients presenting more than 24 hours postingestion with evidence of hepatotoxicity.

b. Limitations to use of the Rumack-Matthew nomogram include the following (Ann Emerg Med 2007;50:292-313):
   i. Presentation more than 24 hours postingestion
   ii. An unknown or unreliable history of ingestion
   iii. Overdoses with extended-release formulations
   iv. Chronic or repeated supratherapeutic ingestions
   v. Patients with preexisting hepatic disease, chronic alcohol use, or concurrent medications metabolized by the CYP system or that alter gastric motility.



Nomogram: acetaminophen plasma concentration vs time after acetaminophen ingestion (adapted with permission from Rumack and Matthew. *Pediatrics.* 1975;55:871-876). The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose (Rumack et al. *Arch Intern Med.* 1981;141(suppl):380-385).

Figure 1. Rumack-Matthew nomogram.

Reprinted from: Tylenol for Healthcare Professionals. Guidelines for the Management of Acetaminophen Overdose. McNeil Consumer & Specialty Pharmaceuticals. Available at www.tylenolprofessional.com/guidelines-and-studies.html.

5. Intravenous acetylcysteine is advantageous because of its decreased overall administration time (21 hours vs. 72 hours for oral) and minimal GI adverse effects. If intravenous acetylcysteine formulation is not available and cannot be obtained in a timely fashion, poison control centers can be contacted for instructions on compounding the inhalational acetylcysteine formulation for intravenous use. It is not recommended to use this strategy except for emergencies.
6. Oral acetylcysteine is dosed for 18 total doses; doses may be repeated if emesis occurs within 1 hour of a dose. Two oral formulations exist. One preparation is an effervescent tablet that must be dissolved in water before administration, and the other is a liquid preparation that may be diluted in juice or carbonated beverages to improve palatability. Antiemetics may be administered if significant nausea or vomiting occurs. Table 4 discusses the dosing strategies for oral and intravenous administration of acetylcysteine.
    a. For exceptionally large ingestions (e.g., over 30 g), some studies have recommended alternative approaches:
        i. An increased dose of acetylcysteine (Med J Aust 2020;212:175-83).
        ii. Given that acetaminophen is dialyzable, intermittent hemodialysis is an option (Clin Toxicol 2014;52:856-67). This approach would also require an increase in the acetylcysteine dose (i.e., 2-fold) due to its concurrent increased clearance (Clin Toxicol 2016;54:519-22). However, a dosing adjustment does not appear to be necessary in the setting of continuous veno-venous hemofiltration (*Clin Toxicol*. 2015;53(10):941-949).
7. Although treatment guidelines recommend 18 total doses of acetylcysteine administered throughout 72 hours for oral acetylcysteine therapy and 21 hours of the intravenous infusion of acetylcysteine, many poison control centers recommend early discontinuation if the following conditions are met (or prolonged therapy if they are not met) (Ann Emerg Med 2007;50:280-1):
    a. Serum acetaminophen concentrations are undetectable or less than 10 mcg/mL.
    b. ALT concentrations are normal (60 IU/L or less) or improving. Some clinicians also advocate for an international normalized ratio (INR) of 1.3 or less.
    c. The patient is clinically improved.
8. Adverse effects (intravenous): Anaphylactoid reactions (rash, urticarial, pruritus) that are often infusion rate-associated, hyponatremia, hypervolemia, seizures (pediatric patients with unadjusted volume)
9. Adverse effects (oral): Nausea, vomiting, anaphylactoid reactions (rare)
10. Patients experiencing mild anaphylactoid reactions (rash, pruritus, flushing) can be effectively treated with diphenhydramine, and acetylcysteine therapy can be resumed.
11. Medication errors may occur because of the complex dosing regimens (Ann Pharmacother 2008;42:766-70). Common errors include delays in therapy, incorrect dosages, and incorrect infusion rates. To mitigate these errors, some institutions have developed a a 2-step, and even 1-step, intravenous regimen (Toxicol Commun 2018;2:81-4; *Br J Clin Pharmacol.* 2021;87(5):2399-2400).

Table 4. Acetylcysteine Dosage

Route	Dose
Oral	**Loading dose:** 140 mg/kg **Maintenance doses:** 70 mg/kg every 4 hr for a total of 17 doses (72 hr)
Intravenous	**Loading dose:** 150 mg/kg (max 15 g)[a] in 200 mL of 5% dextrose in water infused for 60 min **Maintenance dose:** 50 mg/kg (max 5 g)[a] in 500 mL of 5% dextrose in water infused for 4 hr followed by 100 mg/kg (max 10 g)[a,b] in 1000 mL of 5% dextrose in water infused for 16 hr Patients weighing < 40 kg require reduced volume administration

[a] Dose limits are provided by the manufacturer; however, small retrospective studies have shown that acetylcysteine is well tolerated when using actual body weight for patients > 100 kg and exceeding the recommended max doses (Am J Ther 2016;23:e714-9.)(Am J Ther 2014;21:159-63).

[b] Higher ongoing infusion rates (e.g., 200 mg/kg over 16 hr) may be required for massive paracetamol ingestions (i.e., initial concentration that is double the standard nomogram line) and a clinical toxicologist should be consulted (Chiew AL, Reith D, Pomerleau A, et al. Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust 2020;212:175-183. doi: 10.5694/mja2.50428).

D. Monitoring
   1. Patients should be monitored for improvement in vital signs and mental status.
   2. The following laboratory values should be monitored periodically for improvement as well as for potential worsening.
      a. ALT, aspartate aminotransferase (AST), total bilirubin, INR, and prothrombin time
      b. Acetylcysteine may cause a dose-dependent decrease in prothrombin time, although this has no clinical effect on coagulation
      c. BUN and SCr
      d. Serum electrolytes
      e. Fulminant hepatic failure: Serum bicarbonate, serum sodium, serum lactate, arterial blood gas, serum glucose, and ammonia concentrations

Patient Case

Questions 2 and 3 pertain to the following case.
A 42-year-old woman (height 66 inches, weight 79.2 kg [176 lb]) presents to the ED with the chief concern of flu-like symptoms. Her symptoms include headache, congestion, severe nausea and vomiting, abdominal pain, and some confusion. She has been taking acetaminophen 500-mg caplets as needed for her symptoms, but she just ran out of the bottle she purchased yesterday. On presentation, she is alert and oriented. Her vital signs are as follows: BP 135/90 mm Hg, HR 83 beats/minute, RR 18 breaths/minute, and temperature 101.8°F (38.8°C). An acetaminophen concentration on admission was 100 mcg/mL, AST 560 IU/L, and ALT 310 IU/L. The physician wants to begin general management.

2. Which general management strategy is most indicated for this patient?
   A. 10% magnesium citrate 240 mL per tube once
   B. Continued stabilization of the patient and good supportive care
   C. Gastric lavage
   D. Charcoal 50 g once

3. Which is the most appropriate treatment for her acetaminophen toxicity?
   A. Give acetylcysteine 11,200 mg oral bolus, followed by 5600 mg orally every 4 hours for 17 doses.
   B. Give acetylcysteine 11,200 mg intravenous bolus, followed by 5600 mg intravenously every 4 hours for 12 doses.
   C. Give acetylcysteine 12,000 mg intravenously over 1 hour, followed by 4000 mg intravenously over 4 hours; then 8000 mg intravenously over 16 hours.
   D. Acetylcysteine therapy is not indicated in this patient.

V. SALICYLATES

A. Background
   1. Salicylates as a single agent (not in combination with other agents) accounted for 6595 overdoses and 18 deaths in 2022. These numbers, which include overdoses of both adult and pediatric formulations of acetylsalicylic acid, are often underreported because these products are not typically recognized as a potential cause.
   2. However, because of the development of child-resistant containers, aspirin overdose causing accidental death in children has reduced drastically. (Lancet 1977;2: 289-90)

B. Clinical Presentation
   1. The mechanism of toxicity for salicylates is through the interference with aerobic metabolism owing to the uncoupling of mitochondrial oxidative phosphorylation, leading to increases in anaerobic metabolism, which causes a significant lactic acidosis (Emerg Med Clin North Am 2007;25:333-46). This also leads to hypoglycemia because of glycogen depletion, gluconeogenesis, and catabolism of proteins and free fatty acids. Salicylates also directly stimulate the respiratory center, leading to hyperventilation and respiratory alkalosis. Secondary complications from hyperventilation include dehydration and compensatory metabolic acidosis.

2. Salicylates are readily absorbed in the stomach and small intestine and are then conjugated with glycine in the liver to the active component, salicylic acid. In overdoses, the liver cannot metabolize the excess drug, and most is then excreted unchanged by the kidneys (Postgrad Med 2009;121:162-8).
3. The most common clinical symptoms associated with a salicylate overdose are hyperventilation (causing respiratory alkalosis), tinnitus, and GI irritation. Symptoms may vary depending on the serum salicylate concentration; however, these may be low to normal early in the presentation (Postgrad Med 2009;121:162-8):
   a. Serum concentration less than 30 mg/dL: Asymptomatic
   b. Serum concentration 15–30 mg/dL: Therapeutic concentrations
   c. Serum concentration 30–50 mg/dL: Hyperventilation, nausea, vomiting, tinnitus, dizziness
   d. Serum concentration 50–70 mg/dL: Tachypnea, fever, sweating, dehydration, listlessness
   e. Serum concentration greater than 70 mg/dL: Coma, seizures, hallucinations, stupor, cerebral edema, dysrhythmias, hypotension, oliguria, renal failure
4. Acute salicylate toxicity is typically associated more with GI symptoms; chronic toxicity is more associated with CNS-type symptoms.
5. Absorption may be delayed up to 36 hours because of gastric pylorospasm, bezoar formation (precipitate concretions because of poor solubility), or enteric-coated formulations; therefore, these ranges should be used with caution because they may not correlate with actual symptoms (Am J Emerg Med 2010;28:383-4).

C. Treatment
1. There is no antidote for salicylate poisoning; the goals of therapy are to limit the additional absorption of salicylates and to provide supportive care.
2. Maintain a patent airway and assist ventilation, if necessary. Ensure adequate ventilation to prevent respiratory acidosis; however, do not mechanically ventilate patients unless clinically necessary as this will interfere with the patient's ability to appropriately compensate and maintain pH.
3. Gastric decontamination with a single dose of activated charcoal is recommended within 60 minutes of acute ingestions and if the patient is alert with the absence of vomiting. However, there may be a role for administration after this time frame, as well as multidose administration based on the characteristics of the ingestion.
4. Administer intravenous crystalloid fluids at a rate of 10-20 mL/kg/hr for the first 2 hours to maintain a normal BP and a urine output of 1–1.5 mL/kg/hr.
5. Administer intravenous glucose for hypoglycemia or significant neurologic symptoms.
6. Urine alkalinization is recommended to enhance renal elimination and increase the glomerular filtration rate.
   a. The following administration strategies have been described in the literature:
      i. Administer 250 mL of sodium bicarbonate 8.4% over 1 hour; then administer additional 50-mL boluses as needed to maintain a goal urine pH range of 7.5–8.5.
      ii. Administer a continuous infusion of 150 mL of sodium bicarbonate 8.4% in 1 L of 5% dextrose in water at 2–3 mL/kg/hour to maintain a urine output of 1–2 mL/kg/hour. Do not allow the serum pH to fall below 7.4.
   b. Oral bicarbonate is not recommended because it may enhance salicylate absorption by accelerating tablet dissolution.
   c. Discontinue bicarbonate once the serum salicylate concentrations are less than 30 mg/dL or there is a resolution of clinical symptoms.
7. Alkaline diuresis will increase potassium secretion, and hypokalemia will make it more challenging to raise the urine pH. Adequate potassium concentrations should be aggressively maintained.

8. Consider hemodialysis for any of the following (Postgrad Med 2009;121:162-8):
    a. Acute renal insufficiency
    b. End-organ damage (severe pulmonary edema, seizures, rhabdomyolysis)
    c. Altered mental status
    d. Deterioration of clinical status
    e. Severe acid-base disturbances
    f. If hemodialysis is not effective, hemoperfusion and continuous renal replacement therapies may be considered (Ann Emerg Med 2015;66:165-81).

D. Monitoring
1. Patients should be monitored for up to 24 hours because of the possibility of delayed or impaired absorption.
2. Monitor RR, and support as needed; caution is advised if intubation is required because of a requirement for an increased minute ventilation (Am J Emerg Med 2010;28:383-4).
3. During urine alkalinization, monitor for signs and symptoms of fluid overload, hypernatremia, hypokalemia, hypocalcemia, and worsening alkalemia.

Patient Case

4. A 62-year-old man presents to the ED with the chief concern of nausea, tachypnea, and flu-like symptoms. He is alert and oriented and can communicate that his symptoms have been worsening for the past 2 days. He has been taking a combination cold product, which he thinks has helped. His medical history is significant for a stroke, for which he takes aspirin 325 mg by mouth daily, and hypertension, for which he takes amlodipine 5 mg by mouth daily. His vital signs are as follows: BP 135/82 mm Hg, HR 78 beats/minute, RR 29 breaths/minute, and temperature 100.2°F (37.9°C). Arterial blood gas results are as follows: pH 7.52, P_{CO_2} 25, and HCO_3 20 mEq/L. A salicylate concentration is sent, which is 25 mg/dL. Which treatment management strategy is most indicated for this patient?
    A. Sodium chloride infusion
    B. Urgent endotracheal intubation
    C. Sodium bicarbonate infusion
    D. Hemodialysis

VI. OPIOIDS

A. Background
1. Opioids as a single agent (not in combination with other agents) accounted for 20,392 overdoses and 346 deaths in 2022. The Centers for Disease Control and Prevention reports that almost 15,000 deaths are caused by prescription opioid painkillers annually.
2. The most common agents associated with a toxicologic event were fentanyl (prescription and nonprescription), heroin, oxycodone, buprenorphine, and tramadol.
3. The most common agents associated with a toxicologic death were fentanyl (prescription and nonprescription), heroin, oxycodone, methadone, and morphine.
4. Opioids act at the mu, delta, and kappa opioid receptors, although mu is responsible for most of the opioids’ clinical effects.

B. Clinical Presentation
  1. The most common clinical symptoms associated with opioid overdose are respiratory depression (defined as fewer than 12 breaths/minute), coma, miosis, and hypoactive bowel sounds.
  2. Additional findings may include stupor, hepatotoxicity, acute renal failure, rhabdomyolysis, compartment syndrome, hypothermia, and seizures (N Engl J Med 2012;367:146-55).
  3. Diagnostic workup is as follows: (Pharmacotherapy: A Pathophysiologic Approach, 9e. New York: McGraw-Hill, 2014):
     a. 12-lead ECG to assess for QT prolongation (methadone may cause QT prolongation leading to torsades de pointes).
     b. Arterial blood gas to assess for respiratory acidosis
     c. Standard chemistry panel for electrolyte and glucose abnormalities as well as Creatine kinase (CK), BUN, and SCr for signs of rhabdomyolysis
     d. Pulse oximetry

C. Treatment
  1. Stabilize the airway, provide supplemental bag-valve mask respirations if needed, and administer supplemental oxygen. Establish an airway, if needed, by endotracheal intubation.
  2. Administer intravenous crystalloid fluids to maintain BP.
  3. Gastric decontamination with a single dose of activated charcoal may be considered only if the patient presents within the first hour after exposure and is awake with an intact airway. Whole bowel irrigation can be considered for extended-release formulations or for “packers” of illicit substances (including ingestion of fentanyl patches).
  4. Antidote therapy (N Engl J Med 2012;367:146-55; Circulation 2023;148:e149-84):
     a. Naloxone is a competitive antagonist at the opioid receptor.
     b. The intravenous route is preferred, but naloxone is also effective through the endotracheal, intramuscular, intranasal, inhalational, intraosseous, or intrapulmonary route. However, it is important to note that the bioavailability and onset of action can vary greatly between different routes.
     c. Onset of action of intravenous naloxone is 1–2 minutes, with a duration of 30–120 minutes.
     d. Dosing may be affected by the specific opioid agent and dose, affinity for the mu-receptor, and patient weight. Goal of care is reversal of ventilatory depression, not necessarily reversal of neurologic depression, as this is more likely to precipitate acute opioid withdrawal syndrome.
     e. Initial dose is 0.04 mg in adult patients and 0.1 mg/kg in pediatric patients; if no response, the dose is increased every 2–3 minutes to 0.5 mg, 2 mg, 4 mg, and 10 mg, followed by 15 mg. Large doses (eg, 10 mg intravenously) and frequent repeat administration of naloxone are necessary for patients thought to have had an overdose of certain combinations of agents such as heroin laced with carfentanil and fentanyl combined with xylazine (*Cureus*. 2024;16(4):e57638).
     f. It is recommended that a continuous infusion be initiated at a dose of two-thirds the effective bolus dose per hour (0.04–4 mg/hour) for patients requiring subsequent naloxone doses to sustain effect secondary to exposure to long-acting opioids (e.g., methadone) or a sustained-release product (Ann Emerg Med 1986;15:566-70).
     g. Intranasal administration appears to be safe and effective when the intravenous route is not available. The dose is administered by attaching a 2 mg/2 mL naloxone prefilled syringe to an atomizer and spraying an equal portion (1 mL) of the contents into each nostril. Commercial preparations contain up to 4 mg per actuation.

  h. Adverse effects are rare and may be more related to a return of sympathetic response to opioid withdrawal. Nausea and vomiting are common and can lead to aspiration. If the situation allows, providing assisted manual ventilation prior to administering naloxone can potentiate the sympathetic response to opioid reversal (Anesth Analg 1988;67:730-6).
  i. If no effect is seen at the higher naloxone doses, consider other causes such as co-ingestants or alternative agents.

D. Monitoring – Observe respiratory status and vital signs for a minimum of 4 hours after the last dose of naloxone or discontinuation of the continuous infusion. The duration of a naloxone continuous infusion will vary based on the quantity, pharmacokinetics, and pharmacodynamics of the opioid exposure, in addition to patient specific factors. Closely monitor for signs and symptoms of opioid withdrawal syndrome, such as anxiety, piloerection, heightened sensation to pain, abdominal cramps, diarrhea, and insomnia.

VII. LOPERAMIDE

A. Background
  1. A nonprescription antidiarrheal medication with a 91% increase in reported abuse in 2010-2015 resulting in 15 deaths (Ann Emerg Med 2017;69:73-8). Loperamide as a single agent (not in combination with other agents) accounted for 695 overdoses and 1 death in 2022.
  2. Relatively safe at therapeutic doses; however, can be fatal when high doses are ingested for its euphoric effects
  3. Phenylpiperidine opioid that slows intestinal transit time by stimulating mu-opioid receptors in the GI tract and blocks intestinal calcium channels
  4. Toxicity of loperamide involves blockade of sodium channels and potassium channels in the cardiac tissue, causing QT prolongation and QRS interval widening and leading to life-threatening dysrhythmias and cardiac death

B. Clinical Presentation
  1. Common signs/symptoms include respiratory depression, nausea, vomiting, decreased level of consciousness, miosis, decreased bowel motility/ileus, palpitations, and syncope.
  2. In severe toxicity, ECG findings are abnormal, including widened QRS interval and prolonged QT interval.
  3. Diagnostic workup
    a. 12-lead ECG to assess for QT prolongation and QRS interval widening and development of ventricular dysrhythmias
    b. Arterial blood gas to monitor for respiratory acidosis secondary to respiratory depression
    c. Standard chemistry panel for electrolyte and glucose abnormalities, plus CK, BUN, and SCr for signs of rhabdomyolysis
    d. Pulse oximetry

C. Treatment
  1. Stabilize the airway and provide supplemental oxygen, if needed. Establish an airway if patients cannot protect their airway or have significant respiratory depression.
  2. Administer intravenous crystalloid fluids to maintain BP.

3. Gastric decontamination with a single dose of activated charcoal may be considered only if patients present within 2-4 hours after a large overdose and can protect their airway.
4. Antidote therapy (*Ann Emerg Med.* 2017;70(2):245-252):
   a. Naloxone
      i. Should be administered in addition to supportive care in patients with respiratory depression who cannot protect their airway
      ii. The lowest effective dose should be used; repeat doses may be necessary secondary to loperamide's slow elimination.
   b. Sodium bicarbonate
      i. May be beneficial in patients with signs and symptoms of cardiac toxicity and QRS interval widening secondary to sodium channel blockade by loperamide
      ii. Sodium bicarbonate 1-2 mEq/kg intravenously should be administered concomitantly with magnesium and potassium chloride if electrolyte abnormalities exist.

D. Monitoring
   1. Patients should be closely monitored for resolution of clinical symptoms, including respiratory status, vital signs, and return to baseline mental status.
   2. Monitor serum electrolytes, blood glucose, and 12-lead ECG periodically.
   3. Closely monitor for signs and symptoms of opioid withdrawal.

VIII. ALCOHOLS (METHANOL AND ETHYLENE GLYCOL)

A. Background
   1. Alcohol poisonings (methanol and ethylene glycol) are not as common as poisonings with other substances, accounting for <1% of all cases in 2022 (*Clin Toxicol.* 2023;61(10):717-939), but they can be serious and potentially fatal.
   2. Methanol is commonly found in products such as windshield washer fluid, antifreeze, brake and carburetor fluids, and cooking products.
   3. Ethylene glycol is commonly found in products such as antifreeze, de-icing solutions, refrigerants, and brake fluids.
   4. Toxicity of both agents is caused by the breakdown to toxic metabolites by alcohol dehydrogenase and aldehyde dehydrogenase.
      a. Methanol is converted to formaldehyde and then to formic acid, which results in an anion gap acidosis and ocular toxicity.
      b. Ethylene glycol is converted to glycoaldehyde and then to glycolic acid, followed by glyoxylic acid, and, eventually, oxalic acid. Glycolic acid results in an anion gap acidosis and CNS toxicity. Oxalic acid results in CNS toxicity and renal toxicity because of the formation of calcium oxalate crystals.

B. Clinical Presentation
   1. Common symptoms include inebriation, altered mental status, nausea, vomiting, hematemesis, nystagmus, and depressed reflexes. In rare cases of ethylene glycol toxicity, patients may present with tetany caused by hypocalcemia. Symptoms typically develop over the first 24 hours; however, they can be delayed for days in the setting of ethanol coingestion.

2. Early in therapy, an osmolar gap will be present, but this will diminish as the parent compound is metabolized.
   a. As the osmolar gap declines, the anion gap will rise, resulting in a significant metabolic acidosis.
   b. Calculations:
      i. Osmolar gap (OG):
      Measured osmolality - calculated osmolality (normal OG less than 10)
      ii. Calculated osmolality:
      (sodium x 2) + (glucose/18) + (BUN/2.8)
      iii. Calculated osmolality with ethanol ingestion:
      (sodium x 2) + (glucose/18) + (BUN/2.8) + (ethanol/4.6)
      iv. Calculated osmolality with methanol ingestion:
      (sodium x 2) + (glucose/18) + (BUN/2.8) + (methanol/3.2)
      v. Calculated osmolality with ethylene glycol ingestion:
      (sodium x 2) + (glucose/18) + (BUN/2.8) + (ethylene glycol/6.2)
      vi. Anion gap (AG; normal 8-12 mEq/L):
      $Na - (Cl + HCO_3)$
3. Methanol and ethylene glycol serum concentrations may be monitored to determine severity and to guide therapy in conjunction with an anion gap metabolic acidosis. Often, the ability to obtain these serum concentrations is not readily available and may take several hours to perform; therefore, therapy should not be delayed for lab results.

C. Treatment
1. Treatment is focused on blocking the toxic alcohol metabolism and allowing it to be excreted unchanged in the urine. Treatment is recommended when serum methanol or ethylene glycol concentrations exceed 20 mg/dL, the patient has a documented history of ingestion, there is a high clinical suspicion of ingestion combined with an osmolal gap >10 mOsm/kg, or there is a presence of an anion gap metabolic acidosis of unknown etiology.
2. Gastric decontamination is not recommended.
3. Fomepizole is the preferred antidote because of its predictable response, ease of dosing, and lack of contraindications to use.
   a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.
   b. Dosing is a 15-mg/kg intravenous bolus (as a loading dose); then 10 mg/kg every 12 hours for four doses; then 15 mg/kg every 12 hours until methanol/ethylene glycol concentrations are less than 20 mg/dL.
   c. After 48 hours, fomepizole induces its own metabolism, requiring dosage increases.
   d. Oral administration is effective and may be considered if intravenous access cannot be established (Clin Toxicol 2008;46:181-6).
   e. Therapy is discontinued when methanol/ethylene glycol concentrations are less than 20 mg/dL. If the patient is still symptomatic with a normal pH, further workup is warranted, and hemodialysis may be indicated.
   f. Hemodialysis increases the clearance of fomepizole; therefore, doses must be administered every 4 hours during hemodialysis. Continuous renal replacement therapy has also been found to increase the clearance of fomepizole, and although guidance regarding dosing adjustments is limited and requires further investigation, current data suggest reducing the maintenance dose by half as compared with hemodialysis (*Clin Toxicol.* 2022;60(4):451-457).
   g. Adverse effects may include headache, nausea, dizziness, abdominal pain, hypotension, and bradycardia.

4. Ethanol may be administered by diluting 95% alcohol for intravenous, oral, or per-tube administration.
   a. Mechanism of action is competitive inhibition of alcohol dehydrogenase.
   b. Alcohol dehydrogenase has a higher affinity for ethanol.
   c. Intravenous alcohol preparations are no longer commercially available and must be compounded.
   d. Initial dosing is 600–700 mg (7.6–8.9 mL/kg) of a 10% solution, followed by an infusion of 66 mg/kg/hour (0.83 mL/kg/hour). The infusion dose may be initiated at 154 mg/kg/hour (1.96 mL/kg/hour) in chronic drinkers. The goal is to maintain a serum ethanol concentration of 100 mg/dL (0.1%) until symptoms have diminished and methanol or ethylene glycol serum concentrations are undetectable. (Ann Emerg Med 2009;53:439-50).
   e. Disadvantages include frequent monitoring and ICU admission in some institutions.
   f. Adverse effects include CNS depression, nausea, vomiting, abdominal pain, polyuria, and hypoglycemia (especially in children).
5. Hemodialysis should be considered if the clinical condition deteriorates, as evidenced by:
   a. Methanol/ethylene glycol concentration greater than 50 mg/dL
   b. Significant metabolic acidosis
   c. Development of acute renal failure (ethylene glycol) or visual disturbances (methanol)
   d. Development of significant electrolyte abnormalities
6. Additional therapies
   a. Pyridoxine and thiamine
      i. Serve as cofactors in the metabolism of the toxic metabolites of ethylene glycol to nontoxic metabolites
      ii. Pyridoxine promotes the metabolism of glyoxylate to glycine.
         (a) Dosing is generally recommended to be one or more intravenous doses of 50 mg
      iii. Thiamine promotes the metabolism of glycolic acid to a nontoxic metabolite and is also used to prevent or treat Wernicke-Korsakoff syndrome.
         (a) Dosing is generally recommended as 100 mg intravenously, although a concomitant history of chronic alcohol use may warrant use of higher doses (e.g., 500 mg).
   b. Folinic acid
      i. Serves as a cofactor in the metabolism of the toxic metabolites of methanol to nontoxic metabolites. May reduce formate accumulation and reduce the development of metabolic acidosis (Crit Care Clin 2012;28:661-771).
         (a) Dosing is generally recommended to be 1 mg/kg (maximum of 50 mg) intravenously at 4-hour intervals
      ii. Folic acid may be used if folinic acid is unavailable.
   c. Dextrose
      i. Recommended to check a point-of-care level blood glucose concentration before administration (Crit Care Clin 2012;28: 661-771)
      ii. Administer 50 mL of 50% dextrose in water if blood glucose is 70 mg/dL or less or if testing is unavailable.
   d. Magnesium – Recommended to administer 1–2 g intravenously for hypomagnesemia (more common in chronic alcohol use)
   e. Antiseizure medications
      i. Benzodiazepines are the preferred emergent agents to treat seizures.
      ii. Subsequent urgent control therapy can be implemented with intravenous fosphenytoin, valproate sodium, phenobarbital, or levetiracetam.
         (a) Phenytoin and fosphenytoin would not be recommended for patients with a history of chronic ethanol ingestion due to enhanced phenytoin metabolism (*Clin Pharmacol Ther*. 1981;30(3):390-397.

(b) An analysis of a subset of patients in the Established Status Epilepticus Treatment Trial (ESETT) presenting with toxin-related status epilepticus found that a single dose of a second-line antiseizure medication (ie, levetiracetam, fosphenytoin, valproate) was only effective 42% of the time, with both fosphenytoin and valproate performing particularly poorly (*Ann Emerg Med*. 2022;80(3):194-202).

D. Monitoring
  1. Patient should be closely monitored for resolution of clinical symptoms and return to baseline mental status.
  2. Monitor serum electrolytes and blood glucose periodically.
  3. Arterial blood gases with a goal of pH greater than 7.2
  4. Methanol/ethylene glycol concentrations with a goal of less than 20 mg/dL
  5. Monitor the osmolar and anion gaps to ensure the toxic alcohol and metabolites are being cleared appropriately.

Patient Cases

5. A 35-year-old man is admitted to the ED appearing inebriated. He is alert but oriented only to person. His vital signs are BP 122/80 mm Hg, HR 82 beats/minute, and RR 25 breaths/minute. His serum ethanol concentration is 20 mg/dL, and his ethylene glycol concentration is 100 mg/dL. Which is the most appropriate therapy at this time?
   A. Fomepizole
   B. Ethanol infusion
   C. Thiamine
   D. Activated charcoal

6. A patient with methanol intoxication is initiated on fomepizole treatment together with hemodialysis. After the 15-mg/kg bolus dose is given, which would be best for adjusting the maintenance fomepizole doses during dialysis?
   A. 10 mg/kg every 12 hours
   B. 20 mg/kg every 12 hours
   C. 10 mg/kg every 4 hours
   D. 20 mg/kg every 4 hours

IX. ALCOHOL WITHDRAWAL

A. Background
  1. Alcohol withdrawal is a relatively common consequence of hospital admission.
  2. The strongest risk factor is a history of alcohol withdrawal.
     a. Additional tools have been developed, such as the Prediction of Alcohol Withdrawal Severity Scale, to help identify patients at risk for alcohol withdrawal before development of severe symptoms (Alcohol 2014;48:375-90).

B. Clinical Presentation
  1. Withdrawal symptoms typically occur within 8 hours after blood alcohol concentrations decrease, peak at 72 hours, and are markedly reduced at 5–7 days (N Engl J Med 2014;371:2109-13).

2. Common symptoms include tremors, diaphoresis, nausea, vomiting, and abnormal vital signs, including hypertension, tachycardia, hyperthermia, and tachypnea (Am J Emerg Med 2013;31:734-42).
3. Additional symptoms categorized as moderate to severe withdrawal include:
    a. Alcoholic hallucinations – Auditory, visual, or tactile; may last up to 6 days
    b. Alcohol withdrawal seizures (tonic-clonic) – Occur within 72 hours; however, it is highest in the first 24 hours after the last drink.
    c. Delirium tremens – Severe and potentially life-threatening symptom that may develop within 72 hours; presentation includes autonomic hyperactivity, confusion, delirium, psychosis, hallucinations, and seizures.

C. Treatment
1. The goal of therapy is to keep the patient safe, alleviate and prevent the progression of symptoms, and treat comorbidities (Crit Care Med 2010;38(suppl):S494-S501). Agents for the treatment of alcohol withdrawal are listed in Table 5.
2. Benzodiazepines are the primary agents used in treatment; they bind to the γ-aminobutyric acid ($GABA_A$) receptor, resulting in hyperpolarization and membrane stabilization.
    a. Lorazepam and diazepam are preferred because of their advantageous pharmacokinetic and pharmacodynamic profiles, most notably their longer durations of action compared with other benzodiazepines.
    b. Chlordiazepoxide is not recommended in the acute stabilization setting.
    c. Symptom-triggered therapy is preferred because it reduces benzodiazepine use, duration of mechanical ventilation, and duration of ICU stay.
        i. A front-loading regimen (i.e., a single dose of preventative medication) is recommended for patients at high risk for severe withdrawal (J Addict Med 2020;14:1-72).
    d. Scheduled treatment may be necessary if symptoms are severe or difficult to control.
3. Use of ethanol to control alcohol withdrawal is controversial and is not routinely recommended.
4. Phenobarbital
    a. Barbiturate with sedative, hypnotic, and antiseizure activity. Increases the binding of GABA to $GABA_A$ receptor and prolonging the chloride channel opening. It may also concomitantly mitigate neuronal stimulation through NMDA receptor antagonism. Potential advantage over benzodiazepines in alcohol withdrawal because it does not require GABA to be effective (GABA may be depleted), and a longer duration of action.
    b. Historically considered a second-line agent if benzodiazepines fail to adequately control symptoms. Current data suggests that phenobarbital appears to have equivalent outcomes as that of benzodiazepines, and may be more advantageous for certain patients based on patient-specific factors (Am J Emerg Med. 2023 Jul;69:65-75.)
    c. May increase the efficacy of benzodiazepines when used in combination by increasing the binding to the $GABA_A$ receptor.
5. Clonidine: α_2-receptor agonist that helps control the catecholamine surge associated with withdrawal (responsible for elevations in BP and HR); however, it will not prevent seizures.
6. Baclofen: Selective $GABA_B$ receptor agonist that reduces the signs and symptoms of alcohol withdrawal; however, it will not prevent seizures.
7. Gabapentin: Increases GABA syntheses and concentrations; may reduce benzodiazepine requirements; however, it may not effectively control seizures when used as monotherapy (Ann Pharmacother 2015;49:897-906).
8. Propofol
    a. General anesthetic acting through $GABA_A$ receptor agonism and N-methyl-D-aspartate (NMDA) receptor antagonism; chronic alcohol use is associated with an up-regulation of NMDA.
    b. Useful for controlling delirium and preventing seizures; patients must be intubated to receive propofol for this indication

9. Dexmedetomidine
    a. α_2-receptor agonist, which may help control BP and HR; however, it will not prevent seizures.
    b. May reduce overall benzodiazepine requirements; however, it lacks the activity necessary to prevent seizures.
    c. Recommended when clonidine cannot be administered and as adjunct therapy
10. Ketamine: NMDA antagonist; may reduce overall benzodiazepine use and can be considered in patients refractory to other therapies (Crit Care Med 2018;46:e768-71).
11. Supportive care: Alcohol-dependent patients are often nutritionally deficient and at risk of Wernicke encephalopathy and hypomagnesemia. High dose intravenous folic acid, thiamine, and magnesium should be administered to nutrient-deficient patients. Dextrose containing fluids may also be considered (Crit Care Med 2016;44:1545-52).

D. Monitoring
1. Clinical Institute Withdrawal Assessment for Alcohol Scale (revised version) (CIWA-Ar) or the Minnesota Detoxification Scale (MINDS) to determine the severity of symptoms and treatment
2. A sedation score, such as the Richmond Agitation-Sedation Scale, should be used in place of the CIWA in intubated patients to guide benzodiazepine dosing.
3. Vital signs every 2–4 hours
4. Electroencephalogram for sustained seizure-related activity

Table 5. Agents for Treatment of Alcohol Withdrawal

Agent	Suggested Starting Dose	Suggested Interval/Infusion Dose Range
Diazepam	5–20 mg PO/IV	Every 6–8 hr
Lorazepam	2–4 mg PO/IV	Every 4–6 hr
Phenobarbital	65– 260 mg or 10 mg/kg IV	Every 15–20 min until symptoms are controlled
Clonidine	0.1–0.3 mg PO	Every 8–12 hr
Baclofen	5–10 mg PO	Every 8–12 hr
Gabapentin	600–800 mg PO	Every 8 hr
Propofol	10–20 mcg/kg/min IV	20–70 mcg/kg/min
Dexmedetomidine	0.2–0.4 mcg/kg/hr IV	0.4–1.5 mcg/kg/hr
Ketamine	0.15–0.2 mg/kg/hr IV	0.2–0.3 mg/kg/hr
Thiamine	100–500 mg IV	Every 8–24 hr for 3–5 days
Folic acid	1–5 mg IV	Once daily for 3–5 days
Magnesium	1–4 g IV	Once daily for 3–5 days

IV = intravenously; PO = orally or per tube.

X. β-BLOCKERS AND CALCIUM CHANNEL BLOCKERS

A. Background
1. Cardiovascular agents accounted for a little more than 110,000 toxic exposures in 2022 and were a leading cause of death secondary to pharmaceutical exposure.
2. Two of the most common cardiovascular agents involved in single-agent toxic exposures were β-blockers (28,547 cases and 23 deaths in 2022) and calcium channel blockers (15,718 cases and 30 deaths in 2022).

B. Clinical Presentation
   1. β-Blocker overdoses are characterized by hypotension, bradycardia, and prolonged atrioventricular conduction.
   2. Calcium channel blocker overdoses with the non-dihydropyridine agents are characterized by hypotension, prolonged atrioventricular conduction, bradycardia, lethargy, hyperglycemia, and depressed consciousness. The dihydropyridine agents act peripherally and are primarily associated with vasodilation, hypotension, and reflex tachycardia. However, this receptor selectivity is lost at high doses for both categories (Ann Emerg Med 1993;22:196-200).

C. Treatment
   1. Consider gastric lavage or activated charcoal if patients present within 1–2 hours of overdose. Whole bowel irrigation is recommended for delayed presentation or for sustained- or extended-release formulations.
   2. Maintenance of hemodynamic stability
      a. Goal of therapy is a mean arterial pressure greater than 65 mm Hg or systolic blood pressure (SBP) greater than 90 mm Hg.
      b. Administer isotonic fluids (0.9% sodium chloride or lactated Ringer solution) at 20–30 mL/kg (preferred) or colloidal solutions (e.g., albumin 5% 250 mL).
   3. Administer intravenous calcium chloride or calcium gluconate (first line therapy for calcium channel blocker toxicity).
      a. Calcium chloride 1–2 g (central line is preferred; however, bolus doses may be administered in a peripheral line if needed)
      b. Calcium gluconate 3–6 g. Repeat dose may be given every 15–30 minutes; may also consider continuous infusion at 0.3–0.7 mEq/kg/hour.
   4. Consider sodium bicarbonate for QRS widening, severe acidosis, or dysrhythmia: 1– 2 mEq/kg bolus; may consider a continuous infusion if symptoms persist.
   5. Treat symptomatic bradycardia and hypotension as follows:
      a. Atropine 0.5–1 mg intravenously; if no response, continue to the following options:
      b. Glucagon 5–10 mg (100 mcg/kg) intravenous push for 1 minute (consider for β-blocker toxicity only). If symptom response is achieved from the bolus, may consider a continuous intravenous infusion initiated at the same rate (milligrams per hour) as the bolus dose that achieved response.
         i. Stimulates adenylate cyclase, which increases intracellular cAMP (cyclic adenosine monophosphate), leading to increased inotropy, chronotropy, and cardiac conduction
         ii. Adverse effects include nausea, vomiting, and hyperglycemia. Consider premedicating with an antiemetic intravenously before bolus dosing of glucagon to decrease the risk of nausea and vomiting.
         iii. Use with caution with decreased mental status because of possible aspiration or airway obstruction (also causes lower esophageal sphincter relaxation).
         iv. Not recommended as a preferred treatment option for calcium channel blockers because of limited efficacy and cost
      c. Norepinephrine continuous infusion initiated at 2–5 mcg/minute (0.1 mcg/kg/minute) and titrated to target blood pressure in the setting of vasodilatory shock
      d. In the presence of cardiogenic shock, epinephrine and dobutamine are the agents of choice. Epinephrine continuous infusion should be initiated at 1 mcg/minute (0.01–0.1 mcg/kg/minute) and titrated to target hemodynamic parameters. Dobutamine continuous infusion should be initiated at 2–20 mcg/kg/min and titrated to target hemodynamic parameters. Dopamine is not recommended in this setting.
      e. Transcutaneous or transvenous pacing or intra-aortic balloon pumps may be required in refractory cases

6. Hyperinsulinemic euglycemic therapy (HIET)
   a. Mechanism of action:
      i. Insulin increases the plasma concentrations of ionized calcium, improves the hyperglycemic acidotic state, improves the myocardial use of carbohydrates, and exerts an independent inotropic effect (Am J Crit Care Med 2007;16:498-503).
      ii. Dextrose prevents the development of hypoglycemia after insulin administration.
      iii. Potassium prevents the development of hypokalemia after insulin administration.
      iv. Onset of action is as soon as 5 minutes; however, it may take up to 30 minutes for full effects to be seen.
   b. HIET administration (Clin Toxicol 2011;49:277-83; Am J Health Syst Pharm 2006;63:1828-35; Circulation 2023;148:e149-84):
      i. If baseline glucose is less than 200 mg/dL, administer 50 mL of 50% dextrose in water before insulin administration; may consider an infusion of 10%–20% dextrose to maintain a serum glucose concentration greater than 100 mg/dL
      ii. Correct hypokalemia before initiating insulin therapy. Maintain normokalemia with potassium replacement during insulin infusion and after withdrawal.
      iii. Bolus 1 unit/kg of regular insulin intravenously, followed by a continuous intravenous infusion at 0.5–1 unit/kg/hour; increase rate every 10 minutes to a maximum of 10 units/kg/hour.
         (a) HIET should be continued until existing vasopressor therapy is weaned and hemodynamic stability is obtained. Then, HIET should be tapered over several hours while monitoring for hemodynamic deterioration. Dextrose therapy likely must be continued after discontinuation of HIET to prevent hypoglycemia.
   c. Adverse effects: Hypoglycemia, hypomagnesemia, and hypokalemia
   d. Monitoring:
      i. Vital signs every 15–60 minutes with a goal mean arterial pressure greater than 65 mm Hg and a HR greater than 50 beats/minute
      ii. Serum glucose every 15 minutes; then every 30–60 minutes once stable to target serum concentrations greater than 100 mg/dL
      iii. Serum potassium every hour during the insulin infusion; then every 6 hours to maintain concentrations above 2.8 mEq/L
      iv. Monitor for fluid overload and iatrogenic hyponatremia. Utilization of more concentrated dextrose infusions (e.g., 50% dextrose) and more concentrated insulin infusions (e.g., 16 units/mL) may be necessary.
7. Intravenous lipid emulsion (J Emerg Med 2015;48:387-97; J Med Toxicol 2017;13:124-5)
   a. Mechanism of action is not well known; however, it is thought to be owing to a combination of binding lipid-soluble agents and the provision of free fatty acids that increase cardiac energy and intracellular calcium.
   b. Improves HR and may reduce mortality as an individual treatment or in combination with other therapies.
   c. Evidence is limited to animal models and human case reports, and its role in therapy is controversial.
   d. Administration:
      i. Bolus of 1.5 mL/kg of 20% lipid emulsion (such as Intralipid) over 2-3 minutes (typical dose is usually 100 mL)
      ii. A repeat bolus may be considered if no response after initial bolus
      iii. The bolus may be followed immediately by an infusion of 20% lipid emulsion at a rate of 0.25 mL/kg/minute. After 3 minutes at this infusion rate, the infusion rate may be adjusted to 0.025 mL/kg/minute (i.e., 1/10 the initial rate) if there has been a significant response; total duration is not to exceed 6 hours.

   - iv. BP, HR, and other available hemodynamic parameters should be recorded at least every 15 minutes during the infusion.
   - v. Adverse effects may include pancreatitis, jaundice, coagulopathies, interference with laboratory results, and fat embolism.
   - vi. Drug interactions are not well known.

Patient Case

Questions 7 and 8 pertain to the following case.
A 52-year-old man is admitted to the ED with concerns about dizziness and headache. His vital signs are as follows: temperature 98.9°F (37.2°C), BP 87/50 mm Hg, and HR 58 beats/minute. His wife reports that he has a history of hypertension and that he was recently given a diagnosis of being in the early stages of Alzheimer disease. She has brought his medications with her; the 1-month supply was refilled 2 days ago: a bottle of diltiazem CD 120 mg/day (7 tablets remaining) and a bottle of donepezil 5 mg once daily (28 tablets remaining).

7. Which decontamination strategy would provide the most benefit?
   - A. Charcoal 25 g every hour until his BP improves
   - B. Ipecac 30 mL, followed by 240 mL of water
   - C. Polyethylene glycol-electrolyte solution 1500 mL/hour until the rectal effluent is clear
   - D. Magnesium citrate 240 mL, followed by 240 mL of water

8. Which antidote would be best to administer first?
   - A. Calcium chloride 1 g intravenously over 1 minute
   - B. Glucagon 5 mg intravenously over 1 minute
   - C. Atropine 2 mg intravenously over 1 minute
   - D. Epinephrine 1 mg intravenously over 1 minute

XI. DIGOXIN

A. Background
1. The cardiac glycosides accounted for 1051 single-agent toxic exposures and 29 deaths in 2022.
2. Mechanism of action is inhibition of the sodium-potassium adenosine triphosphatase pump and suppression of the atrioventricular node.
3. Because of its narrow therapeutic index, toxicity has been reported in as many as 35% of patients receiving digoxin (Postgrad Med 1993;69:337-9).
   - a. The normal therapeutic range is 0.8–2.1 ng/mL.
   - b. Toxicity may be related to an acute ingestion or may be an issue with chronic use in renal dysfunction.
4. Risk factors for digoxin toxicity include renal failure, advanced age, ischemic heart disease, left ventricular dysfunction, electrolyte imbalances (hypokalemia, hypomagnesemia, hypercalcemia), and hypothyroidism (Postgrad Med 1993;69:337-9).

B. Clinical Presentation
  1. Cardiac effects associated with digoxin toxicity include second- and third-degree heart block, tachyarrhythmias, and bradyarrhythmias. More specific examples include fascicular tachycardia, ventricular bigeminy, and ventricular tachycardia (Am J Cardiol 1992;69:108G-119G).
  2. Noncardiac effects associated with digoxin toxicity include nausea and vomiting, lethargy, headaches, confusion, and visual disturbances.

C. Treatment
  1. Consider decontamination strategies if patients present within 2 hours of overdose.
    a. Multidose activated charcoal is beneficial because of the enterohepatic recirculation of digoxin. Load 50–100 g; then 10 g/hour, 10–20 g every 2 hours, or 40 g every 4 hours (Postgrad Med 1993;69:337-9).
    b. Colestipol or cholestyramine is an effective drug-binding alternative to charcoal, but it may not be useful in acute toxicity (Am J Cardiol 1992;69:108G-119G).
    c. Hemodialysis is not considered effective.
  2. Correct serum electrolyte abnormalities.
    a. Correct serum potassium concentration to a goal of 3.5–4 mEq/L.
    b. Correct serum magnesium concentration to a goal of 1.5–2.2 mg/dL.
    c. Correct serum calcium concentration to a goal of 8.5–10.5 mg/dL.
  3. Treat symptomatic bradyarrhythmias with atropine 0.5 mg intravenously.
  4. Digoxin immune antigen-binding fragments (Fab)
    a. Antibodies that bind to digoxin molecules that are then renally excreted
    b. Indications for use in acute intoxications (Crit Care Clin 2012;28:527-35; Circulation 2023;148:e149-84):
      i. Life-threatening arrhythmias: asystole, ventricular fibrillation or tachycardia, complete heart block, symptomatic bradycardia
      ii. Evidence of end-organ damage (e.g., renal failure, altered mental status)
      iii. Hyperkalemia (greater than 5–5.5 mEq/L)
    c. Products:
      i. Digibind (Digoxin Immune Fab): 38 mg per vial
      ii. DigiFab (Digoxin Immune Fab): 40 mg per vial
    d. Dosing:
      i. If amount of digoxin ingested is unknown: 10–20 vials for acute toxicity or 6 vials for chronic toxicity
      ii. If the amount of digoxin ingested is known:
      Dose (vials) = total body load (0.8 × mg of digoxin ingested)/0.5
      iii. If digoxin concentration is known:
      Dose (vials) = [serum digoxin concentration (ng/mL) × weight (kg)]/100
      iv. May consider lower doses of 1 or 2 vials (40–80 mg) for acute ingestions with repeat doses if necessary
    e. Adverse effects include heart failure exacerbation, atrial fibrillation, orthostatic hypotension, hypokalemia, and phlebitis.

D. Monitoring
  1. Monitor vital signs every 30–60 minutes initially. Goal HR of greater than 60 beats/minute and asymptomatic
  2. Monitor serum potassium concentrations hourly for at least the first 6 hours.

3. Additional serum digoxin concentrations are not recommended after the administration of digoxin immune Fab. Minimal change in serum concentrations will be expected as the digoxin laboratory test will still measure the bound, inactive digoxin molecules. Fab-digoxin complexes may stay in the serum for several days. Repeat serum digoxin concentrations may be checked 24 hours after the initial treatment if Fab is not administered.

XII. ANTIDEPRESSANTS

A. Background
   1. Antidepressants accounted for more than 63,974 single agent toxic exposures and 56 deaths in 2022.
   2. Some of the most common agents involved in toxic exposures were the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs).
   3. SSRIs block the reuptake of serotonin at the presynaptic neuron.
   4. Patients with SSRI overdoses are often asymptomatic with self-limiting effects (Emerg Med Clin North Am 2007;25:477-97). The most common adverse effects may include drowsiness, tremor, altered mental status, nausea and vomiting, tachycardia, hypotension, seizures, and QRS- or QT-interval prolongation.
   5. TCAs exert many effects, including blocking the reuptake of norepinephrine and serotonin at the presynaptic neuron, blocking muscarinic cholinergic receptors, blocking antihistamine effect, blocking the sodium channel, and, to a lesser degree, blocking α-adrenergic receptors.
   6. Individuals with TCA overdoses may present with the following (Emerg Med Clin North Am 1994;12:533-47):
      a. Cardiovascular: Hypo- or hypertension, tachy- or bradycardia, increased QRS or QT interval, atrioventricular-conduction block, complete heart block
      b. Respiratory: Hypoventilation, crackles, hypoxia
      c. Neurologic: Delirium, lethargy, seizures, coma
      d. Other: Hyperthermia, dry mucous membranes, urinary retention, blurred vision

B. Treatment
   1. There are no specific antidotes for antidepressant overdoses; general supportive care is recommended, with a focus on ABC.
   2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure (Emerg Med Clin North Am 2000;18:637-54).
   3. Administer crystalloid or colloid fluids to maintain BP and HR, with the goal of a mean arterial pressure >65 mmHg, a SBP greater than 90 mm Hg, and a HR greater than 60 beats/minute.
      a. Norepinephrine or epinephrine may be used if fluid resuscitation alone is unsuccessful.
      b. Dopamine may not be an effective agent because endogenous norepinephrine stores are depleted in an overdose.
   4. Sodium channel blockade
      a. Alkalinization of blood to a pH of 7.45–7.55 is recommended for the TCAs to resolve metabolic acidosis and improve cardiac symptoms. Requires frequent monitoring of arterial pH (varies by effect, but as often as every 15–30 minutes). Sodium load may overcome TCA blockade of sodium channels by increasing the electrochemical gradient.
      b. Administer sodium bicarbonate
         i. Recommended bolus dose of 1 mEq/kg (minimum: 50 mEq) intravenously
         ii. May repeat bolus every 15 minutes until ECG stabilized or arterial pH goal achieved.

        - iii. May consider a continuous infusion of hypertonic saline in patients with refractory cardiac conduction despite optimal serum alkalinization by increasing sodium load.
    - c. Proposed indications for sodium bicarbonate include the following (Chest 2008;133:1006-13; Circulation 2023;148:e149-84):
        - i. QRS greater than 100–120 milliseconds
        - ii. Wide complex tachycardia
        - iii. Cardiac arrest
        - iv. Right bundle-branch block
        - v. Refractory hypotension
    - d. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation is present. Magnesium replacement is recommended for membrane stabilization in patients with a QTc greater than 500 milliseconds and normal serum magnesium concentrations.
    - e. Seizures should be managed with benzodiazepines. Phenobarbital and propofol may be considered if the patient is refractory to benzodiazepines and has a stable BP.
        - i. Phenytoin and lacosamide are not recommended because of their effects on sodium channels and cardiac adverse effects, respectively.
    - f. Intravenous fat emulsion
        - i. Many case reports for use in amitriptyline and SSRI overdose
        - ii. Administration (use lean body mass):
            - (a) Bolus of 1.5 mL/kg of 20% lipid emulsion (Intralipid) over 1–5 minutes (typical dose is usually 100 mL for patients weighing 70 kg and more)
            - (b) May repeat up to two times for persistent cardiovascular collapse
            - (c) Bolus doses should be followed by an intravenous infusion of 0.25–0.5 mL/kg/minute for 60 minutes (typical dose is 18 mL/minute for a 70 kg patient)
            - (d) Continue for up to 10 minutes after cardiovascular recovery.

- C. Monitoring – Patients should be monitored for clinical improvement for at least 6–8 hours and for a minimum of 24 hours for more severe adverse effects or with citalopram or escitalopram (because of the longer half-lives of these agents).
    - a. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, troponins, BP, and HR.
    - b. Monitor for signs and symptoms of respiratory depression with RR and pulse oximetry.

- D. Serotonin Syndrome
    1. Excessive serotonin concentrations lead to overstimulation of serotonin-1A and serotonin-2A receptors in the central and peripheral nervous systems (Emerg Med Clin North Am 2007;25:477-97).
    2. Adverse effects include altered mental status, autonomic instability (hyperthermia, tachycardia, hypertension, arrhythmias), and neuromuscular changes (hyperreflexia, increased rigidity).
    3. Diagnosis is made according to clinical findings; many clinicians support the use of the Hunter Serotonin Toxicity Criteria (QJM 2003;96:635-42). By this method, patients are likely to have serotonin toxicity if they have taken a serotonergic agent and one of the following criteria are present:
        - a. Spontaneous clonus
        - b. Inducible clonus PLUS agitation or diaphoresis
        - c. Ocular clonus PLUS agitation or diaphoresis
        - d. Tremor PLUS hyperreflexia
        - e. Hypertonia PLUS temperature above 100.4°F (38°C) PLUS ocular clonus or inducible clonus
    4. Treatment should focus on supportive care with intravenous fluids; symptoms typically resolve within 24–48 hours.
        - a. Discontinue the offending agent.
        - b. Benzodiazepines should be administered as first line for agitation and muscle rigidity.

   c. Cyproheptadine is a histamine-1 receptor antagonist and nonspecific serotonin receptor antagonist. A single dose of 8–12 mg by mouth should be administered for agitation and muscle rigidity as an adjunct to benzodiazepines. A second dose may be administered in 6–8 hours if symptoms persist.
   d. If condition worsens, may require intubation with continuous infusion benzodiazepines
   e. Although not well studied, case reports have shown the efficacy of dexmedetomidine at doses of 0.05–0.8 mcg/kg/hour (in pediatric patients).

Patient Case

9. A 21-year-old man is admitted to the ED after taking 30 citalopram 20-mg tablets about 2 hours ago. His vital signs are as follows: BP 125/85 mm Hg, HR 77 beats/minute, RR 15 breaths/minute, and temperature 98.7°F (37.1°C). Which is the best intervention for this patient?
   A. Administer lorazepam 2 mg intravenously to prevent seizure activity.
   B. Administer cyproheptadine 8 mg by mouth to prevent muscle rigidity.
   C. Recommend a cooling blanket to prevent serotonin syndrome–related hyperthermia.
   D. Order a 12-lead ECG to monitor for cardiac conduction disturbances.

XIII. ATYPICAL ANTIPSYCHOTICS

A. Background
   1. The atypical antipsychotic agents accounted for about 16,541 toxic exposures and 17 deaths in 2022.
   2. These agents are classified primarily as having D2-dopaminergic receptor and serotonin-2A receptor antagonism. Additional effects include antagonism of the α_1- and histamine-1 receptors.
   3. Adverse effects associated with the atypical antipsychotics are typically self-limiting.
      a. More severe adverse effects may include CNS depression, tachycardia, hypotension, and QT prolongation.
      b. Less severe adverse effects include dizziness, drowsiness, miosis, blurred vision, urinary retention, and CNS excitation.

B. Treatment
   1. There are no specific antidotes for the atypical antipsychotics; general supportive care is recommended, focusing on ABC.
   2. Gastric decontamination is not typically recommended; however, single-dose activated charcoal may be administered within the first hour of exposure if no contraindications exist (J Emerg Med 2012;43:906-13).
   3. Administer crystalloid to maintain BP with a goal mean arterial blood pressure >65 mm Hg, an SBP greater than 90 mm Hg, and an HR greater than 60 beats/minute.
      a. Consider vasopressors if fluid resuscitation is inadequate.
      b. Because of the α-receptor antagonist activity of these agents, norepinephrine or phenylephrine is preferred if vasopressors are needed.
   4. Administer sodium bicarbonate if QRS prolongation is present (quetiapine overdose only)
   5. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation. Magnesium replacement is recommended for membrane stabilization in patients with a QTc greater than 500 milliseconds and normal serum magnesium concentrations.

6. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
7. Anticholinergic symptoms can potentially be treated with IV physostigmine (or oral/patch formulations of centrally acting acetylcholinesterase inhibitors in the setting of a shortage) in select patients (e.g., normal ECG); however, substantial controversy exists with this approach, particularly in the setting of a concomitant TCA overdose and its overall functional use considering its short half-life (Ann Emerg Med 2000;35:374-81). Currently, it is not frequently used and further investigations into its safety and efficacy are necessary (J Med Toxicol 2015;11:179-84).
8. Lipid emulsion therapy may be effective because of the high lipophilicity of these agents and may be considered if more traditional treatment means do not improve the cardiovascular complications of decreased HR and/or BP (J Emerg Med 2012;43:906-13). Administer an intravenous bolus dose of 1.5 mL/kg of 20% lipid emulsion over 2–3 minutes, followed by a continuous intravenous infusion of 0.25–0.5 mL/kg/min for 60 minutes, if necessary.

C. Monitoring: Patients should be monitored for clinical improvement for at least 8–12 hours.
   1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
   2. Monitor for respiratory depression with RR and pulse oximetry.

XIV. LITHIUM

A. Background
   1. Lithium was associated with almost 3341 toxic exposures and seven deaths in 2022.
   2. Mechanism of action is through an influence on serotonin and norepinephrine reuptake, inhibition of the phosphatidylinositol cycle, and inhibition of the post-synaptic D2 receptor.
   3. Adverse effects associated with lithium include:
      a. Acute overdose:
         i. GI: Nausea, vomiting, diarrhea
         ii. CNS: Confusion, tremor, myoclonus, seizures, coma
         iii. Cardiovascular: T-wave inversion, ventricular arrhythmias
      b. Chronic adverse effects:
         i. Endocrine: Hypothyroidism, myxedema coma
         ii. Nephrogenic diabetes insipidus

B. Treatment
   1. There are no specific antidotes for lithium; general supportive care is recommended, focusing on ABC.
   2. Gastric decontamination is not typically recommended in toxic acute ingestions. Single-dose activated charcoal is not effective for lithium overdoses; whole bowel irrigation may be beneficial.
   3. Administer crystalloid to maintain BP, with a goal SBP greater than 90 mm Hg. Consider vasopressors if fluid resuscitation is not adequate.
   4. Replace serum electrolytes, especially magnesium and potassium, if QT prolongation is present.
   5. Seizure activity should be managed with benzodiazepines, barbiturates, or propofol.
   6. Lithium overdoses are primarily managed with fluid resuscitation and renal replacement therapy.
      a. Saline infusions may be administered if there are no contraindications to fluid therapy (goal is a serum sodium concentration of 140–145 mEq/L). Lithium clearance is reduced in hyponatremia.
      b. Intermittent hemodialysis may require several sessions to fully remove lithium concentrations because of the rebound of lithium concentrations that occurs after dialysis sessions. Consider continuous renal replacement therapy (CRRT) for hemodynamically unstable patients.

c. Suggested indications for the use of hemodialysis include (Chest 2008;133:1006-13):
    i. Severe toxicity (severe altered mental status or seizures)
    ii. Renal failure (cannot eliminate lithium)
    iii. Lithium concentrations greater than 2.5 mmol/L in chronic exposures
    iv. Lithium concentrations greater than 4 mmol/L in acute exposures

C. Monitoring – Patients should be monitored for clinical improvement for at least 8–12 hours.
1. Monitor for cardiac toxicity with a 12-lead ECG, CK-MB, and troponins.
2. Monitor for respiratory depression with RR and pulse oximetry.
3. Monitor renal function with urine output, BUN, and SCr.
4. Monitor baseline lithium concentrations and then every 6 hours after until concentrations have decreased to less than 1.5 mmol/L (normal 0.6–1.2 mmol/L).

Patient Case

10. A 24-year-old woman is brought to the ED by her roommate. She has been in a normal state of health, but the roommate is concerned because she “seems really out of it.” According to the roommate, the patient had an appointment with the physician today, and she had been given a prescription to refill olanzapine 5 mg by mouth daily, but the bottle is empty. On physical examination, she is alert and oriented person, place and time but she dozes off several times. Her vital signs are stable, and a 12-lead ECG shows sinus tachycardia. Which intervention is most appropriate for this patient?

A. Lactated Ringer solution 500 mL intravenously
B. 8.4% sodium bicarbonate 50 mL intravenously
C. Lorazepam 2 mg intravenously
D. Clinical monitoring for 6 hours

XV. ORAL HYPOGLYCEMICS

A. Background
1. Oral hypoglycemics accounted for 5944 single-agent exposures and 29 deaths in 2022.
2. The most common oral hypoglycemic involved in toxic exposures was metformin, followed by the sulfonylureas and the glucagon-like peptide-1 (GLP-1) receptor agonists.
3. The most serious adverse effects were reported with the sulfonylureas; however, most fatalities were associated with metformin.

B. Clinical Presentation
1. Clinical signs and symptoms include hypoglycemia (not with metformin), nausea, vomiting, dizziness, tachycardia, and diaphoresis.
2. More severe adverse effects include seizures, palpitations, tachyarrhythmias, electrolyte abnormalities, and metabolic (lactic) acidosis.

C. Treatment
1. Stabilization of the ABC
2. Identifying the causative agent is important because specific treatment will vary by the agent involved.
3. Consider gastric decontamination with single-dose activated charcoal if patients present within 1 hour of overdose.
4. Observe clinically asymptomatic patients for a minimum of 8 hours (Am J Health Syst Pharm 2006;63:929-38).

5. For symptomatic patients or blood glucose less than 70 mg/dL, treat with glucose:
    a. Conscious patients: Administer 8 oz of an oral carbohydrate (such as juice, non-diet sodas, or milk) or oral glucose tablets or gels.
    b. Unconscious patients: Administer intravenous dextrose, 0.5–1 g/kg
    c. Repeat doses may be required; consider a continuous infusion of dextrose if needed. Glucose concentrations should be monitored often (every 15–60 minutes) until stable.
    d. Use caution to avoid overcorrection of serum glucose.
6. Octreotide
    a. Mechanism of action is a somatostatin analog that inhibits the secretion of insulin.
    b. Primarily studied in sulfonylurea overdose, but considered a treatment option for all oral hypoglycemic toxic exposures
    c. Administer 50 mcg subcutaneous or intravenous, followed by 50-mcg doses every 6 hours. Intravenous dextrose infusion should be slowly tapered off.
    d. Adverse effects include headache, dizziness, nausea, abdominal pain, and sinus bradycardia.
7. Sodium bicarbonate
    a. Indicated for severe metformin-associated lactic acidosis
    b. 1–2 mEq/kg or 50–200 mEq of 8.4% sodium bicarbonate intravenously
8. Glucagon
    a. Mechanism of action is stimulation of gluconeogenesis.
    b. May trigger additional insulin secretion, leading to a secondary hypoglycemia
    c. May provide benefit in prehospital settings when oral or intravenous options are not available, but is not routinely recommended
    d. Not recommended in pediatric patients, in malnourished patients, or for sulfonylurea toxic exposures
9. Hemodialysis or continuous renal replacement therapy may be necessary to enhance metformin clearance in severe cases.

D. Monitoring
  1. Regular assessment of vital signs and mental status (Emerg Med J 2006;23:565-7)
  2. Measure capillary blood glucose at a minimum of every hour for 24 hours with a goal of greater than 70 mg/dL.
  3. Measure BP hourly, especially after octreotide administration.

Patient Case

11. As the pharmacist in the ICU satellite, you receive a call from a distressed nurse about a patient in the cardiac step-down unit. The patient was found unconscious, and, on investigation, it was discovered that he had received a glyburide 20-mg tablet 1 hour earlier that was meant for another patient. The patient has stable vital signs, but his point-of-care blood glucose concentration is 37 mg/dL. Which intervention is most appropriate at this time?

    A. 8 oz of milk by mouth
    B. 50 mL of 50% dextrose in water intravenously
    C. Octreotide 100 mcg subcutaneously
    D. Glucagon 1 mg intramuscularly

XVI. DRUGS OF ABUSE

A. Background
   1. Miscellaneous stimulants and street drugs accounted for 46,753 toxic exposures and 186 deaths in 2022.
   2. The most common drugs of abuse involved in toxic exposures were amphetamines, marijuana (and derivatives), cocaine, methamphetamines, and heroin.
   3. Total numbers are difficult to determine because few of these agents can be detected with current techniques.

B. Amphetamines/Methamphetamines/MDMA (ecstasy)
   1. Mechanism of action/toxicity: stimulation of the CNS, peripheral release of catecholamines, inhibition of catecholamine reuptake, and inhibition of monoamine oxidase (Intensive Care Med 2004;30:1526-36)
   2. Clinical presentation (Intensive Care Med 2004;30:1526-36)
      a. Common: Confusion, tremor, anxiety, agitation, irritability, mydriasis, tachyarrhythmias
      b. Severe: Hepatocellular necrosis, acute hepatitis, myocardial ischemia, hypertension, cerebral hemorrhage, seizures, hyponatremia
   3. Treatment
      a. Mostly supportive care with intravenous fluid administration and airway maintenance
      b. Gastric lavage or activated charcoal if within 1 hour of ingestion
      c. BP control with benzodiazepines, α-blocker, or vasodilator (e.g., nitroglycerin, nitroprusside, nicardipine). Avoid the use of β-receptor blocking agents because of risk of unopposed α-receptor activity leading to an increase in BP.
      d. Benzodiazepines for agitation, anxiety, psychosis, and/or uncontrolled hypertension titrated to effect. Haloperidol or phenothiazines may be considered for use (with caution) in patients with primary psychiatric disorders or dopamine-mediated movement disorders.
      e. Cooling therapy if hyperthermia present
      f. Monitor for serotonin syndrome.

C. Synthetic Cannabinoids: K2/Spice
   1. Mechanism of action/toxicity: stimulation of the cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors (Pharmacotherapy 2015;35:189-97)
      a. CB1 receptors modulate glutamate and GABA and are found both peripherally and centrally.
      b. CB2 receptors are located in immune tissue and the CNS and modulate pain and emesis.
   2. Clinical presentation (J Pharm Pract 2015;28:50-65)
      a. Predominantly euphoria or excited delirium
      b. Common adverse effects include:
         i. Psychiatric: Agitation, anxiety, hallucinations, paranoia, catatonia
         ii. Neurologic: Cognitive impairment, ataxia, dizziness, headache, seizures
         iii. Cardiovascular: Tachycardia, palpitations, hypertension
         iv. GI: Nausea, vomiting
         v. Renal: Acute kidney injury, rhabdomyolysis
   3. Treatment
      a. Mostly supportive care with intravenous fluid administration
      b. Benzodiazepines for agitation or seizure activity. Antipsychotics for agitation may be considered for use (with caution) in patients with primary psychiatric disorders or dopamine-mediated movement disorders.

D. Cocaine
  1. Mechanism of action/toxicity (Intensive Care Med 2004;30:1526-36):
    a. Potent sympathetic nervous system stimulant
    b. Inhibits the presynaptic reuptake of epinephrine and norepinephrine; also stimulates norepinephrine release
    c. Acts as a reuptake inhibitor of dopamine, norepinephrine, and serotonin
  2. Clinical presentation (Intensive Care Med 2004;30:1526-36)
    a. Predominantly euphoria or excited delirium
    b. Common/severe adverse effects include:
      i. Psychiatric: Agitation, anxiety, psychosis, delirium
      ii. Neurologic: Stroke, subarachnoid or intracranial hemorrhage, seizures
      iii. Cardiovascular: Tachycardia, hypertension, palpitations, arrhythmias, heart failure, aortic dissection
      iv. GI: Gastric ulcers, gastric perforation, bowel ischemia
      v. Respiratory: Status asthmaticus, pulmonary hypertension, pulmonary edema, alveolar hemorrhage
      vi. Renal: Acute kidney injury, rhabdomyolysis
  3. Treatment
    a. Mostly supportive care with intravenous fluid administration
    b. Gastric decontamination is typically not recommended. Activated charcoal may provide benefit if given within 1 hour of oral ingestion.
    c. Benzodiazepines are administered for agitation or seizure activity and titrated to relaxation. Because of their ability to block the CNS stimulant effect of cocaine, benzodiazepines are also an effective treatment for hypertension and tachycardia.
    d. BP control with benzodiazepines, α-blocker, or vasodilator (e.g., nitroglycerin, nitroprusside, nicardipine). Although controversial and devoid of robust empirical evidence, it has been recommended to avoid the use of ϐ-receptor blocking agents because of a risk of unopposed α-receptor activity leading to an increase in blood pressure.

E. Synthetic Cathinones: Bath Salts
  1. Mechanism of action/toxicity: increases presynaptic concentrations of serotonin, dopamine, and norepinephrine by stimulating release and antagonizing monoamine reuptake (Pharmacotherapy 2014;34:745-57)
  2. Clinical presentation (J Pharm Pract 2015;28:50-65):
    a. Predominantly euphoria, increased energy, and alertness
    b. Common adverse effects include:
      i. Psychiatric: Agitation, aggression, anxiety, hallucinations, paranoia
      ii. Neurologic: Amnesia, confusion, insomnia, seizures, dizziness, headache
      iii. Cardiovascular: Angina, hypertension, tachycardia, palpitations
      iv. GI: Abdominal pain, nausea, vomiting, anorexia, hepatic failure
      v. Renal: Acute kidney injury, increased SCr, and rhabdomyolysis
  3. Treatment
    a. Mostly supportive care with intravenous fluid administration
    b. Benzodiazepines or antipsychotics for agitation or anxiety
      i. Haloperidol is an alternative option, but it should be used with caution and close monitoring because of the potential to worsen hyperthermia.
      ii. Consider propofol or dexmedetomidine for severe symptoms.
    c. Antiemetics for nausea and vomiting
    d. Monitor for serotonin syndrome.

F. Piperazines
  1. Mechanism of action/toxicity: enhances neurotransmitter release and reuptake inhibition of dopamine, serotonin, and norepinephrine release (Emerg Med Clin North Am 2014;32:1-28)
  2. Clinical presentation (J Pharm Pract 2015;28:50-65):
     a. Predominantly euphoria and increased energy
     b. Common adverse effects include:
        i. Psychiatric: Agitation, anxiety, hallucinations, psychosis, depressed mood or mood swings, paranoia
        ii. Neurologic: Confusion, insomnia, tremor, seizures, dizziness, headache
        iii. Cardiovascular: Angina, hypertension, tachycardia, palpitations, QT prolongation
        iv. GI: Abdominal pain, nausea, vomiting
        v. Renal: Urinary retention
  3. Treatment
     a. Mostly supportive care with intravenous fluid administration
     b. Benzodiazepines for agitation or seizures
     c. Avoid antipsychotics because of the risk of worsening hyperthermia, extrapyramidal effects, and hypotension or arrhythmias.
     d. Treat hypertension with parenteral antihypertensives or clonidine.
     e. Hyperthermia treatment if above 104°F (40°C)
     f. Monitor for serotonin syndrome.

G. Ketamine
  1. Mechanism of action/toxicity (Lancet 2005;365:2137-45):
     a. Noncompetitive NMDA receptor antagonist (blocks glutamate and aspartate)
     b. Mild to moderate blockade of catecholamine reuptake
  2. Clinical presentation:
     a. Predominantly hallucinations and vivid dreams
     b. Common adverse effects include:
        i. Psychiatric: Impaired memory, cognitive dysfunction, severe agitation
        ii. Cardiovascular: Hypertension, tachycardia, cardiac arrhythmias
        iii. Respiratory: Laryngospasm, apnea, respiratory depression
        iv. GI: Anorexia, nausea, vomiting
        v. Genitourinary: Cystitis, irritable bladder, urethritis
  3. Treatment
     a. Mostly supportive care with intravenous fluid administration
        i. Monitor for rhabdomyolysis
        ii. Aspiration precautions are recommended in comatose patients
        iii. Urinalysis and serum chemistries if symptomatic for cystitis
     b. Activated charcoal may provide benefit if given within 1 hour of oral ingestion. Additional doses every 4 hours may be considered.
     c. Benzodiazepines are recommended for agitation (eg, short-acting agents such as midazolam) or seizures (eg, lorazepam per standard status epilepticus management).
     d. Haloperidol may be used if benzodiazepines are not effective. Monitor closely because of the potential of lowering the seizure threshold and worsening of dystonia, hypotension, neuroleptic malignant syndrome, and/or myoglobinuria.

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ANSWERS AND EXPLANATION TO PATIENT CASES

1. **Answer: B**

The most important first step in all drug overdose cases is to try to stabilize the patient's ABC (Answer B is correct). This may involve the use of supplemental oxygen or advanced airway management, establishment of intravenous access, and administration of intravenous fluids. Once the patient is stable, the process of identifying the suspected toxin can begin (Answer D is incorrect). This may include thoroughly examining the patient, speaking with family or first responders, and communicating with the patient's physicians and pharmacies. Blood and urine samples may be sent for quantitative or qualitative toxicologic assays (Answer A is incorrect). A coma cocktail may provide some benefit, but a clear cause should be established before considering its use (Answer C is incorrect).

2. **Answer: B**

The patient has symptoms of an acute acetaminophen overdose, and stabilizing the patient, together with providing good supportive care, is indicated until a determination for additional therapy can be made (Answer B is correct). Typical decontamination strategies may provide benefit, but they do not definitively improve patient outcome. Magnesium citrate (and cathartics as a whole) is not considered an effective decontamination strategy (Answer A is incorrect). Gastric lavage is of most benefit within the first 60 minutes of exposure, and the potential adverse effects outweigh any potential benefit (Answer C is incorrect). Similarly, single-dose charcoal requires more rapid administration (Answer D is incorrect).

3. **Answer: C**

The patient is considered at high risk of developing hepatic damage from acetaminophen and requires therapy with intravenous acetylcysteine (Answer D is incorrect). The dose of intravenous acetylcysteine is as follows (doses are calculated using actual body weight): loading dose: 150 mg/kg in 200 mL of 5% dextrose in water for 60 minutes; maintenance dose: 50 mg/kg in 500 mL of 5% dextrose in water for 4 hours, followed by 100 mg/kg in 1000 mL of 5% dextrose in water for 16 hours (Answer C is correct and Answer B is incorrect). Oral dosing of acetylcysteine is not a viable option because of the patient's severe nausea and vomiting (Answer A is incorrect).

4. **Answer: C**

This patient has an acute salicylate overdose. Although his serum salicylate concentrations are in the therapeutic range, he has symptoms consistent with salicylate toxicity, as evidenced by his nausea, tachycardia, and respiratory alkalosis. He is currently stable, but his serum salicylate concentrations may continue to rise; therefore, enhanced elimination with serum bicarbonate is the best option (Answer C is correct). His vital signs, which are stable, should be monitored for changes; however, although he is not experiencing signs of significant dehydration, he would benefit from the fluid administration of sodium bicarbonate. Sodium chloride would be more beneficial if his vital signs were more unstable (Answer A is incorrect). His RR, which is elevated, should be monitored; however, he is alert and able to communicate and therefore does not need intubation at this time (Answer B is incorrect). He is also not indicated for hemodialysis because of his moderate symptoms, but this could be considered if his condition deteriorates (Answer D is incorrect).

5. **Answer: A**

The most appropriate therapy for an ethylene glycol intoxication is fomepizole (Answer A is correct). An ethanol infusion is a possible treatment option, but it is not preferred because of the difficulties in dosing and adverse effects (Answer B is incorrect). Thiamine is a cofactor in the metabolism of ethylene glycol, but it would not be preferred to administer thiamine before fomepizole (Answer C is incorrect). Activated charcoal is not an option for gastric decontamination because it is not effective for alcohols (Answer D is incorrect).

6. **Answer: C**

After the initial bolus of fomepizole, 10 mg/kg should be administered every 12 hours. Because of the increased clearance of fomepizole during hemodialysis, the frequency is changed to every 4 hours during dialysis (Answer C is correct and Answer A is incorrect). When dialysis is completed, the dose returns to 10 mg/kg administered every 12 hours; and once the patient has been on 48 hours of therapy, dosing increases to 15 mg/kg because of self-induction. There is no indication for a dose increase (Answer B and D are incorrect).

7. **Answer: C**

The best treatment option for this patient is whole bowel irrigation because of the extended-release formulation of diltiazem (Answer C is correct). Activated charcoal may provide some benefit, but, similar to ipecac, the time interval is not known, and diltiazem does not undergo enterohepatic recirculation (Answer A is incorrect). Ipecac is not recommended because it may impede treatment with more effective treatment options and because it is no longer manufactured in the United States (Answer B is incorrect). A cathartic would not be useful in this situation; guidelines recommend its use only in combination with other decontamination strategies, not as a single agent (Answer D is incorrect).

8. **Answer: A**

There are several potential antidotes for a calcium channel blocker overdose. Calcium is the most effective, and it should be given by bolus, followed by continuous infusion if needed (Answer A is correct). Glucagon is not an effective antidote and is therefore not an option for this patient (Answer B is incorrect). Atropine is effective for symptomatic bradycardia caused by the calcium channel blocker, but the dose should be 0.5–1 mg (Answer C is incorrect). Epinephrine is an alternative to glucagon, but this dose is excessive for a patient not experiencing cardiac arrest (Answer D is incorrect).

9. **Answer: D**

Most of the SSRIs are relatively safe, and many patients will present as asymptomatic after an overdose. However, there is a potential for a patient to develop serious adverse effects, such as serotonin syndrome, seizures, and cardiac toxicity. Although this patient is stable and has no specific concerns, it is recommended to check a 12-lead ECG to measure for QT-interval prolongation and treat with sodium bicarbonate, if necessary (Answer D is correct). A benzodiazepine should be administered if muscle rigidity develops, but it should not be used as a prophylactic measure (Answer A is incorrect). It is recommended that the patient be observed for at least 6–8 hours. Cyproheptadine is only indicated for symptomatic patients (Answer B is incorrect). Measures should be performed to reduce hyperthermia if a serotonergic syndrome develops, but this should be treated with measures to reduce muscle activity (i.e., sedation or chemical paralysis), not by applying measures to enhance surface cooling (Answer C is incorrect).

10. **Answer: D**

Although the patient appears to have taken an overdose of olanzapine, she is experiencing only mild symptoms. The best intervention would be to monitor her for 6 hours for the progression of her symptoms or development of additional complications (Answer D is correct). Intravenous fluids would be appropriate if the patient has dehydration or hypotension (Answer A is incorrect). Sodium bicarbonate is indicated for QRS prolongation and is not warranted at this time (Answer B is incorrect). Olanzapine does not cause seizures; therefore, lorazepam would not be indicated (Answer C is incorrect).

11. **Answer: B**

The most appropriate intervention at this time is to give the patient intravenous dextrose (Answer B is correct). Oral glucose is a viable option, but it cannot be administered to an unconscious patient without oral access (Answer A is incorrect). Octreotide should be reserved for use if the administration of a glucose solution fails to raise the blood glucose above 70 mg/dL for two consecutive readings (Answer C is incorrect). Glucagon is a potential option for treatment, but because the patient has intravenous access, the intramuscular route would not be preferred (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**

The best option for this patient right now is to administer octreotide 50–100 mcg subcutaneously (Answer C is correct). The patient has not responded to two doses of intravenous dextrose, as evidenced by point-of-care glucose concentrations less than 70 mg/dL; therefore, additional doses of dextrose are not indicated (Answer A is incorrect). Although glucagon is also a potential option, it is not recommended for sulfonylurea exposures (Answer B is incorrect). Sodium bicarbonate intravenously may be indicated in this scenario if the patient had metformin-associated lactic acidosis; however, the patient is not on metformin and has no signs of lactic acidosis (Answer D is incorrect).

2. **Answer: A**

Any of the options listed in this question are possible treatments for a patient with a β-blocker overdose who is not responding to the administration of intravenous fluids and calcium. The optimal choice ultimately involves efficacy and appropriate dosing. Glucagon is an option, and it should be dosed at 5–10 mg intravenously initially (Answer A is correct). Atropine is an option for the patient's bradycardia, but the initial recommended dose is 0.5–1 mg intravenously (Answer B is incorrect). Hyperinsulinemic euglycemic therapy may be preferred in this setting; however, the correct bolus dose is 1 unit/kg intravenously (Answer C is incorrect). Dopamine is an option for the treatment of hypotension and bradycardia, but the correct dose would be the initiation of an infusion at 5–10 mcg/kg/minute titrated to effect (Answer D is incorrect).

3. **Answer: B**

Given the patient's presentation and the common toxidromes, the most likely scenario is a cholinergic agent (Answer B is correct). The patient is experiencing bradycardia with a normal BP and RR, has a decrease in mental status, and is experiencing nausea. Although not an absolute, anticholinergics and sympathomimetics are more commonly associated with tachycardia (Answers A and D are incorrect). Similarly, opioids are typically associated with a decrease in respirations (Answer C is incorrect).

4. **Answer: A**

The patient is experiencing QT prolongation after an atypical antipsychotic overdose. It is important to stabilize the patient by administering intravenous sodium bicarbonate and electrolyte replacement (Answer A is correct). Her potassium concentration is low, requiring replacement. Because the time interval of the overdose is not known, there is limited benefit for activated charcoal (Answer B is incorrect). Although her magnesium concentration is normal, it should be monitored; however, her magnesium concentration does not require replacement at this time because her QTc is less than 500 milliseconds (Answer C is incorrect). Lorazepam is not indicated for prophylaxis of seizure activity (Answer D is incorrect).

5. **Answer: A**

This patient has the clinical signs and symptoms of alcohol withdrawal. Management should focus on the patient's safety and controlling his symptoms, and treatment should be administered using a symptom-triggered therapy strategy. The primary agents used to control symptoms are the benzodiazepines, and lorazepam is a good option (Answer A is correct). Barbiturates such as phenobarbital are typically reserved for patients who do not respond to benzodiazepine therapy because of benzodiazepine's long elimination half-life and stronger sedative effects and oral dosing may be difficult with his level of confusion (Answer B is incorrect). Propofol should be avoided in non-intubated patients (Answer C is incorrect). Clonidine is a potential option, especially because this patient has borderline hypertension, but oral dosing may be difficult with his level of confusion (Answer D is incorrect).

6. **Answer: B**

The patient is experiencing an unintended opioid overdose, as evidenced by the decreased RR and decreased consciousness. Administration of the antidote, naloxone, is the best option (Answer B is correct). Because 2 hours have passed since the methadone dose was given, there is limited usefulness for activated charcoal at this time, and it would not be advisable to administer it to an unconscious patient without an established airway (Answer A is incorrect). Whole bowel irrigation is also not useful in this situation because it is too late to prevent drug absorption together with the airway safety concern (Answer C is incorrect). Administration of intravenous fluids would be beneficial to improve BP but should not be administered in this case before naloxone (Answer D is incorrect).

7. **Answer: D**

The patient is not responding to the initiation of intravenous fluids and calcium gluconate, so HIET is warranted. Because of the patient's low serum potassium concentrations, it is critical to replace this before administering insulin (Answer A is incorrect and Answer D is correct). The patient's glucose concentration is greater than 200 mg/dL, so additional glucose need not be given at this time (Answer B is incorrect). Full effects may take up to 30 minutes to be seen, but this should not prevent the initiation of HIET (Answer C is incorrect).

8. **Answer: B**

The patient is not responding to the initiation of intravenous fluids, calcium, and HIET. The most appropriate option at this time would be to increase the rate of the insulin infusion and initiate vasopressor therapy to improve hemodynamic stability in the interim (Answer B is correct). The initial infusion rate is 0.5–1 unit/kg/hour and is titrated every 15–20 minutes until hemodynamically stable. The next option would be to initiate a vasopressor agent (Answers A and C are incorrect). From the choices listed, the best first option is norepinephrine initiated at 4 mcg/minute and titrated to the desired effect. Epinephrine is also a possible option, but it would be recommended if the patient were not responding to increasing doses of norepinephrine. Intravenous lipid emulsion is a potential therapy, but it is typically administered in a patient with severe decompensation caused by a lipophilic medication who is not responding to fluids or vasopressors (Answer D is incorrect).

AMERICAN COLLEGE OF CLINICAL PHARMACY
WORLD HEADQUARTERS

13000 W. 87th Street Parkway
Lenexa, KS 66215-4530
TELEPHONE: (913) 492-3311
E-MAIL: accp@accp.com
www.accp.com